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Center of Excellence – Remote Decentralised Clinical Trials

WP4 – EAGLE

D4.2 SWOT analysis of ethical, legal, and operational barriers and enablers for DCT in the EU

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Document History

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Abstract

Decentralised clinical trials (DCTs) offer many opportunities for improvement in clinical evidence collection, as they provide the opportunity to move traditional trials from the investigative site setting to the participant's context to bring potential benefits from a patient perspective (patient choice, convenience), the ease of conducting a trial (efficiencies, cost), and the ability to collect and collate data in a reliable and resourceful way (digital technologies).

Decentralised (and hybrid) clinical trials are not without uncertainty and debate, and their successful implementation depends to a large extent on stakeholders' acceptance. It is therefore essential to analyse this new operational approach to conducting clinical trials from their perspectives.

For this purpose, a SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis of the key trial activities that differ from traditional procedures was carried out, identifying the main challenges and proposing possible solutions to resolve them. From this SWOT analysis 11 strengths, 14 weaknesses, 2 opportunities and 4 threats were extracted. An expert panel composed of members of the 2 advisory bodies of the Trials@Home project, the External Stakeholder Platform (ESP) and the Patient Expert Panel (PEP), assessed each item and scored it according to the importance they conferred to them, allowing us to identify 6 main challenges for DCTs. Finally, a Delphi study was conducted with external experts to generate and evaluate the best proposals to address these challenges.

The proposed solutions include: 1. Strengthen the health and digital literacy of participants through training and support from research teams and sponsors. Avoid overburdening local resources with such tasks, as well as participants' reliance on peers to answer questions. 2. Addressing threats through clear guidelines, procedural guides, and expert knowledge sharing, Proposals for centralisation of Research Ethics Committee (REC) on a European level, have had a low acceptance. 3. Seizing opportunities by raising awareness among local resources about the value of research for patients.

Implementing these solutions is expected to enhance DCT execution, promoting effective, ethical, and high-quality research outcomes.

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List of Abbreviations

Abbreviations	Meaning
AE	Adverse Event
DCT	Decentralised Clinical Trial
EAGLE	Ethical, regulAtory, Gcp and LEgal aspects
eConsent	Electronic Consent
EFPIA	European Federation of Pharmaceutical Industries and Associations
ePROS	Electronic Patient-Reported Outcomes
ESP	External Stakeholder Platform
EU	European Union
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GCP	Good Clinical Practice
GDP	Good Distribution Practices
HTA	Health Technology Assessment
ICH	International Conference on Harmonization
HCP	Health care provider
IMP	Investigational Medicinal Product
MLCF	MedLawconsult Foundation
PEP	Patient Expert Panel
REC	Research Ethics Committee
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
SWOT	Strengths, Weaknesses, Opportunities, and Threats
TCT	Traditional Clinical Trial
UCB	Union Chimique Belge (UCB Biopharma)
UMCU	University Medical Center Utrecht
UU	Utrecht University

Introduction

Clinical trials are a fundamental pillar of clinical evidence. They represent an advance in medicine and are crucial in the development of new drugs or new indications. Their impact not only extends to the individual patient, but also to the society as a whole by improving medical care (1,2). Conventional or 'Traditional' clinical trials (TCTs) are usually carried out in large hospitals or research centres and over the course of a trial, several face-to-face visits to the facilities are usually required. Their conduct requires considerable effort including time and money from multiple stakeholders. These trials are sometimes difficult to conduct or are not even started because they are not considered feasible. In some cases, low recruitment and difficulties in retaining participants lead to their premature closure, if the objectives are not achieved (3–5). Additionally, the possibility to participate in TCTs may be more limited in areas far from large urban centres, and therefore accessibility for potential participants living in rural areas is limited. Therefore, the traditional trial approach may lead to results less generalisable to the general population (1).

Decentralised clinical trials (DCTs) offer a multitude of possibilities for improvement in the collection of clinical evidence, providing the opportunity to move traditional trials from the investigative site setting to the participant's context in order to bring forward potential advantages from the patient's perspective (choice, convenience), the ease of conducting a trial (efficiencies, cost) and the ability to collect and collate data reliably and resourcefully (digital technologies). Through the use of new technologies, such as mobile applications, electronic devices and web pages, DCTs potentially increase the accessibility and scope of clinical trials, accelerating recruitment and improving retention, because distance to the centre, travel, or the schedule of visits are less of an impediment to participation (1,3). DCTs may also become more representative of the patient population of interest and diverse by opening up the opportunity for participation more broadly through greater geographic reach and accessibility. In addition, DCTs can include the delivery of drugs or medical products directly to the participant, as well as home visits by healthcare professionals.

It is increasingly common for health systems to use digital health technology to collect data and deliver health care services (6,7). Technology can be incorporated into clinical research to improve efficiency, data collection, and data quality (8).

Interest in DCTs has increased because of the health crisis caused by the SARS-CoV-2 virus pandemic, driving the use of technology and non-face-to-face care in both research and clinical practice (3,9). Drug regulatory agencies, research ethics committees, sponsors, and investigators had to make quick decisions to ensure the safety of participants and the integrity of data (10). Telemedicine visits, telephone interactions, and remote assessments were common during the early months of the pandemic, when face-to-face appointments at primary care centres and hospitals were not allowed. There are potential advantages of moving from hybrid-style measures which were temporarily implemented under these circumstances, to a more general acceptance of decentralised elements or even fully DCTs.

Decentralised (and hybrid) clinical trials are not without uncertainty and debate, and their successful implementation depends to a large extent on their acceptance by the stakeholders. Particularly relevant is the opinion and positioning of legislators, regulators, and ethics committee members, which can either give them the necessary impulse or limit their use; together with accumulating experience from sponsors, vendors, health care professionals and trial participants. It is therefore essential to analyse this new operational approach of conducting clinical trials from their perspectives. For this purpose, a SWOT (**S**trengths, **W**eaknesses, **O**pportunities, and **T**hreats) analysis of the key trial activities that vary from traditional procedures was carried out, identifying the main challenges for DCTs and proposing potential solutions to solve them.

This deliverable is divided into three parts:

- Part A contains the SWOT analysis

- Part B contains the identification of the critical challenges

- Part C contains the potential solutions

PART A- SWOT analysis of ethical, legal, and operational barriers and enablers for DCT in the EU

A1. Objectives

General Objectives:

- Identify and analyse **S**trengths, **W**eaknesses, **O**pportunities, and **T**hreats of DCTs from regulatory, legal, and ethical perspective

Specific objectives:

- Define the appropriate type of SWOT analysis to analyse ethical, legal, and regulatory aspects.
- Identify units of analysis based on operational differences between DCTs and TCTs.
- Complete one SWOT matrix for each unit of analysis.
- Calibration of the content of the SWOT matrix.

A2. Methods

In order to carry out the SWOT analysis, a five-step process was used:

A2.1. To define the type of SWOT analysis to be performed:

The SWOT analysis methodology is a scientifically recognised social diagnostic tool that has been used in various disciplines, adapted or modified to the specific context or discipline. For this study, we compared DCTs to TCTs and focused on ethical, legal, and regulatory aspects. The internal factors (strengths and weaknesses) are about how DCTs make it easier or harder to comply with ethical, regulatory, and legal issues than TCTs. External factors (opportunities and threats) refer to how the ethical, legal, and regulatory framework facilitates or hinder the conduct of DCTs.

The SWOT analysis matrix is represented in the table below:

	Positive aspects	**Negative aspects**
Internal factors	*Strengths*: What aspects of DCTs facilitate or enhance compliance with ethical, regulatory, and legal requirements compared to TCTs?	*Weaknesses*: What aspects of DCTs hinder or worsen compliance with ethical, regulatory and legal requirements compared to TCTs?
External factors	*Opportunities*: How do ethical, regulatory and/or legal factors enhance or facilitate the implementation of DCT?	*Threats*: How do ethical, regulatory and/or legal factors limit or hinder the implementation of DCT?

Figure 1. SWOT matrix where initial questions are posed to identify the elements of the SWOT.

A2.2. To identify the units of analysis and the frame of reference to be used in the SWOT analysis.

To enable the analysis, it was determined that rather than considering DCTs as a whole, the focus should be on those activities that involve a potential operational difference between DCTs and TCTs, and that may be challenging or have connotations from the ethical, legal, or regulatory perspective. These activities were referred to as *units of analysis*.

To identify these key activities the guidance of regulatory agencies on the management of clinical trials during the COVID-19 pandemic and the previous work done as part of the Trials@Home project was used (10–13).

The following 8 key activities were identified as units of analysis:

Unit of analysis	Description of the activity
Implementation of decentralised/ remote (electronic) consent	In traditional clinical trials, during the informed consent process, the potential participant receives the study information sheet, which includes, among other aspects, the justification and objectives, procedures, potential risks and benefits, and treatment alternatives. Participants should be given as much time as needed to read it. Subsequently, a face-to-face interview with the investigator takes place, in which the information is explained to the potential participant, it is verified that he/she has understood it. Participants should be given sufficient time and opportunity to address concerns, ask questions and receive answers before (and during) the trial. Finally, the informed consent form is signed by both the participant and the investigator. If this procedure takes place remotely, the informed consent will usually be in electronic format including: the verification of the potential participant's identity, the study information, the interview in a telemedicine visit and the electronic signature.
Decentralised screening of potential trial participants	In traditional clinical trials, after signing the informed consent form in person, the investigator verifies and confirms again that the participant meets the criteria for participation by interviewing him/her and reviewing his/her medical history. Depending on the requirements of the protocol, a physical examination is performed, measurements of vital signs and relevant tests are performed. If this procedure takes place remotely through a telemedicine consultation, it is necessary to establish how the investigator will obtain the relevant information from the participant's medical history. As for the physical examination and assessment of vital signs,

	depending on the study protocol and the electronic devices available, the participant himself may perform certain procedures and send the results to the investigator. It is also possible for a health professional to come to the participant's home to perform the physical examination or ask the participant to visit a local family doctor to perform a complete physical examination and then send the report to the investigator.
Home health visits	In traditional clinical trials the participant travels to the trial site where the clinical trial takes place. In a decentralised trial, certain procedures can be performed remote form site (e.g. at home or place of work) by a health professional, doctor or nurse, thus avoiding the need for the participant to travel to the clinic or site.
Telemedicine visits	In traditional clinical trials, most visits are conducted face-to-face at the trial site. Occasionally follow-up telephone calls may be made to obtain clinical trial safety data. In telemedicine visits, the participant contacts a member of the research team (or vice-versa) via a videoconferencing system.
Self-monitoring	In traditional clinical trials, the required measurements and tests are performed in person at the trial site by healthcare professionals. In a decentralised trial, the participant will be able to perform the measurements and tests remote form site (e.g. at home or place of work), sometimes continuously if a device allows it. Depending on the technology, the volume of data generated may be greater and provided at more regular intervals than in the traditional mode.

Delivery and return of investigational product	In traditional clinical trials, the investigator team either administers the IMP in the trial site or provides it for the participant to take at home according to the established schedule. At the end of the treatment period, any unused investigational product is returned by the trial site to the sponsor or destroyed locally according to the standard operating procedure. In remote clinical trials, there is the possibility that the research team sends the medication to the participant's home, always with complete instructions and training regarding storage, administration schedule, and return conditions.
Clinical trial oversight	In traditional clinical trials, all the clinical trial procedures are carried out at the trial site, so there is proximity and direct contact between the members of the research team and the participant. In decentralised trials, some procedures are performed remote from the trial site (e.g. at the participant's home), either by the participant or by third parties who are not direct members of the research team (e.g., companies with home health nursing services), hence a different work dynamic and professional relationship will be established.
Remote safety monitoring	In traditional clinical trials, safety data are obtained in several ways: by review of the participant´s medical history by the investigator at the times established according to the protocol (which may or may not coincide with the on-site visits at the trial site), through information recorded by the participants in the logbook-diaries provided for this purpose (that will be reviewed by investigator in the next visit at the trial site), by interview with the participants during the on-site visits at the trial site and by spontaneous notification by the participant (if he/she contacts the research team about an event that he/she considers important or is concerned about and according to the training in adverse event reporting that he/she received at each

on-site visit).

In decentralised trials, a participant may still use logbooks / diaries, however, the procedure may be different in that the receipt of safety data may be continuous. Sometimes, the investigator may even receive an alert for an abnormal value in a certain parameter before the participant has objectified it or noticed any symptoms.

A2.2.1. Aspects considered in the SWOT analyses

A2.2.1.1. Ethical, legal, and regulatory framework:

Given that the SWOT analysis focuses on the ethical, legal, and regulatory aspects of DCTs, the following frameworks were used as reference to guide and inform the SWOT analysis, i.e. to identify and assess potential SWOTs of DCTs:

- Ethical aspects: the requirements proposed by Emmanuel et al.(14) for evaluating the ethics of clinical research studies, as well as authoritative international ethical guidelines (see below).

- Legal and regulatory aspects: European regulations, standards of good clinical practice and guidelines of National Competent Authorities, as well as (inter)national professional standards and guidelines (see below).

Ethical framework has been established according to the requirements proposed by Emmanuel et al.(14) for evaluating the ethics of clinical research studies. Those requirements are the following:

(1) value—enhancements of health or knowledge must be derived from the research;
(2) scientific validity—the research must be methodologically rigorous;
(3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects;
(4) favourable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks;
(5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it;

(6) informed consent—individuals should be informed about the research and provide their voluntary consent; and

(7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored."

A2.2.1.2. Authoritative international ethical guidelines

- The WMA Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects(15),

- The WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks(16),

- the CIOMS International Ethical Guidelines for Health-Related Research Involving Humans(17).

The regulatory and legal framework is based on the European regulations; National and international Professional standards and guidelines. The following is a non-exhaustive list of these documents:

<u>European regulations:</u>

a) Regulation (EU) Nº 536/2014 of the European Parliament and of the Council of 16th April 2014 on clinical trials on medicinal products for human use (18)
b) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (19)
c) Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (20)

<u>Standards of good clinical practice and guidelines of National Competent Authorities:</u>

a) International Conference on Harmonization of Good Clinical Practice (ICH GCP) (21,22)
b) Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic (EMA) (23);
c) Decentralised clinical trials (DCTs) with medicinal products in Switzerland

(Version 1.1 ,25 October 2021) (24)

d) The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products (Version 2.0, September 2021) (25)

A2.3. Complete one SWOT matrix for each unit of analysis

During a group discussion with the involved research team members, 8 SWOT matrices (one for each unit of analyses) were filled out taking into account the framework of reference.

We considered it appropriate to use the judgment of research team members as a resource to perform this SWOT analysis for the following reasons:

a) The information on some units of analysis in the literature is insufficient.

b) There is a certain degree of uncertainty resulting from current legislative and technological changes.

c) The identification and assessment of SWOTs involves normative judgement and intersubjective, interdisciplinary consideration.

A group of experts was selected from the EAGLE Working Package of the Trials@Home consortium, taking into account the experts' previous involvement in the project tasks as well as their background. Taking into account the criteria of Kennedy and Price, quoted in Yañez et al. (26), we considered as experts those who can make relevant contributions, given their knowledge or experience. The participants were members of FISABIO, UU, UMCU and MLCF/Foundation Lygature. The group was multidisciplinary and had a wide range of backgrounds, including medical doctor, sociologist, clinical trials coordinator, pharmacists, pharmacoepidemiologists, ethicist, legal experts.

During a workshop, the group identified the differential aspects in the way key activities are carried out in TCTs and DCTs and, taking into account the reference framework, brainstormed the items that would form part of each of the quadrants of the SWOT matrix. Each idea was presented and discussed in the group until the final SWOT matrix was shaped.

From the SWOT analyses of each unit, the general SWOT analysis of the DCTs was

elaborated. For this purpose, the items of the 8 SWOT matrices of the units of analysis were added to an EXCEL sheet and new, more general items were generated to categorise the previous ones on the basis of their common aspects.

A2.4. Review by WP4 members

During the Trials@Home annual meeting (September 2022), the SWOT matrices were presented to the WP4 EAGLE members for review and discussion, and the final versions of the SWOT matrices for each unit of analysis were produced.

A2.5. Calibration of the content of the SWOT matrix

The general SWOT analysis matrix of the DCTs was sent to external ethicists, legal experts and regulators from the project's Scientific Advisory Board (SAB) and the consortium's network for their review.

The aim of the review was to ensure the intelligibility of the items included and that there were no major omissions. The reviewers were provided the list with a short explanation of each item and were asked to add their assessments in a comment box, which could include:

- a suggestion to add or delete any of the items;
- a suggestion to change the position of any item in the matrix (for example from strength to opportunity);
- a suggestion to modify any of the proposed explanations for any of the items.

Feedback was provided by three experts during the calibration phase which resulted in only minor rephrasing of the recommendations. These were implemented before the SWOT matrix was finalised.

A3. Results

A3.1. DCTs SWOT Matrix

Strengths	***Weaknesses***
Potential benefits of using eConsent	Barriers due to the use of digital technologies
Potential benefits of using digital technologies for other study procedures different to eConsent	Lack of face-to-face (on-site) contact
Remote access	Difficulties to verify the identity
More free decision making	Privacy issues
Easier to carry out follow-up actions	Not suitable for all CTs, therapeutic areas, participants, and activities
Less burden for participants	Increased burden and responsibility on participants to do some activities themselves
Possibility to reach more geographically dispersed and diverse populations	Difficulties for the participants to perform the activities themselves
Potential improvement of participants' health and digital literacy skills	More burden or risk-taking for the health care providers
Easier to detect external factors that would go unnoticed in visits performed on site	Difficulties in the management and organization/configuration of the investigator team
Possibility of increasing the data collected for both research and safety monitoring	Difficulties in the management and conservation of the biosamples
Easier to monitor/audit/inspect	Difficulties in the management, conservation and administration of the IMP
	Generation of unnecessary data for the research
	Risk of generating invalid data or with questionable quality
	Dehumanisation of the participant
Opportunities	***Threats***
Harmonisation in the regulation and legislation	Non harmonization of the legislation/acceptance on DCTs
Collaboration with local resources	Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs
	Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs)
	Professional certifications and qualifications are not homogeneous among countries.

Figure 2. Elements identified: 11 strengths 14 weaknesses 2 opportunities and 4 threats.

A3.2. Description of the items

A3.2.1. Strengths

S1. Potential benefits of using eConsent

The use of eConsent has been available for some time in hybrid trials as discussed above. A key strength of DCTs would be to establish a more common acceptance of eConsent, enabling participants to routinely take advantage of the potential benefits that this format offers, including:

- Use of digital multimedia technologies

The use of multimedia elements, especially interactive ones, could potentially improve the overall satisfaction of the potential participant with the process.

- Use of layered approach

The presentation of information in a layered format allows the potential participant to deepen their understanding of those aspects that interest them most or about which they have less knowledge, as well as allowing inclusion of a glossary of terms for those concepts that are more difficult to understand. This can improve the understanding of the information and its appropriateness to the information needs and interests of the potential participant.

- Possibility to offer the information in more than one format

Including some of the information in different formats (e.g. video, web, infographic, pdf document, comic) allows the potential participant to use the one that best suits their preferences, potentially improving their satisfaction and maintaining their interest.

- Possibility to include a quiz

The eConsent makes it possible to include questions, either interspersed with the information (at the end of thematic blocks) or at the end of the information, that allows the person to verify whether they have adequately understood the information. This allows the potential participant to feel more involved in the process, to increase their attention, to emphasize those aspects that are considered most important and to guide the researcher in the conversation by knowing which points they have not understood correctly. In addition,

questions can be accompanied by explanations when the answer is incorrect. It is important and more engaging for the participant that these questions are asked more in a game format than in an exam format.

- Facilitating information consultation and re-consenting

The information provided to the potential participant during the informed consent process should be available for consultation during their participation in the clinical trial and even after the trial has ended. The eConsent format can facilitate consultation if it is hosted on a website, an app or a study portal that can be accessed by the participant through a login process. This would also make it easier to re-consent if needed and to consult the different versions of the consent used during the clinical trial.

S2. Potential benefits of using digital technologies for other study procedures different to eConsent

Digital technologies (such as electronic patient reported outcomes (ePROs), real time monitoring of participants, early detection of AEs and SAEs) have a key role to play as enablers of DCTs, with particular prominence during the screening, telemedicine visits, self-monitoring and remote safety monitoring.

A number of potential benefits derive from their use. They can be grouped according to their nature including:

- Remote access enabled by these technologies (explained in more detail in S3)

They allow scheduling of visits in an easier and more flexible way, since the participant can connect from any place where he/she has a good internet connection and a certain privacy; this avoids unnecessary trips, travel expenses, absence from work, need of childcare or elder care service, etc. giving greater independence and autonomy to the participant and reduces their burden, as they do not require as many visits to the centre and can manage their trial participation from home.

- The number of diverse functionalities that are enabled by the technology

During medical visits more professionals can be included (without losing video and audio quality), as well as caregivers of those participants who, due to their characteristics, require

participation, since in some cases they will be in charge of administering medication or taking vital signs, so they must be trained in the study activities and must be able to attend calls.

The visits can be recorded to review later and obtain a better diagnosis (for example, they can be shared with other professional experts in the field or if the doctor has doubts, they can go to the recording to watch it again without having to bring the participant to the site).

- Increased data generation (related to S10)

Technologies also allow participants to have more insight into their health measures and to perform real-time monitoring, as the e-PROs allow them to record their symptoms on a daily basis and prevent or detect at an early-stage possible Adverse Events (these data are transferred to the research team). Collecting symptoms in real time avoids the loss of data that occurs in traditional visits, since they are scheduled periodically. The collection, storage and analysis of all these data is expected to enhance the generation of Real World Evidence which is becoming an area of increasing interest and importance in clinical research.

The generation of new data also allows for the establishment of new digitally derived endpoints that are potentially more meaningful and better than the existing ones.

S3. Remote access

Remote access increases the availability of clinical trials for more potential participants, as there is no need to live close to the site due to the fact that participants do not have to travel to participate; recruitment is expected to be faster and end sooner. This improved access to the trial may make the patient population more representative of the area of interest, allowing for the generation of Real World Evidence (related to S7).

Being able to carry out visits remotely facilitates scheduling, as visits can be performed from any location that meets minimum requirements that depend on the study itself. This makes it easier to incorporate the clinical trial tasks into the participant's daily routine.

Participants are likely to feel more comfortable, as they can perform the clinical trial tasks (including visits) from a familiar environment where they might feel more relaxed.

As remote access allows people to connect from different locations, several professionals

or caregivers can connect at the same time in the telemedicine call, when necessary.

S4. More free decision making

A person's decision-making process is influenced by a number of factors. Having information more adapted to their needs (see S1) and not having to accept or reject a participation proposal made by a known person face-to-face, facilitates freer decision making in which the potential participant does not feel compromised or potentially coerced. DCTs may therefore provide some broad advantages with respect to helping the participant understand the trial or product or eligibility criteria better by absorbing the information in their own time. Additionally, the process of withdrawing from the study also may become easier as it can be done remotely and without having to interact with another person.

S5. Easier to carry out follow-up actions

In DCTs, some follow-up actions are easier to carry out.

- Informed consent and patient engagement

Re-consent or consultation of information provided during the informed consent process may be facilitated by the use of electronic consent (see S1). In addition, DCTs may facilitate actions such as sharing information about the study with participants during and after study completion or sending informative and motivational messages, which may have positive effects on participant engagement.

- Follow-up visits and question resolution

The use of telemedicine can facilitate the conduct of clinical trial follow-up visits (see S2 and S3), as well as the resolution of questions that may arise to the participant as their participation in the study progresses.

- Self-monitoring and safety monitoring

The technologies used in DCTs (see S2) can facilitate the recording of data and enable real-time monitoring, preventing or detecting early and rapidly any adverse events that may occur.

S6. Less burden for participants

In general, one of the main potential benefits of DCTs is that they will reduce the burden of participants. This burden reduction occurs through several ways:

- Electronic informed consent process and screening:

DCTs allow participants to review information about being included in the trial more easily, reaching a wider population whilst avoiding the need to travel to the site (see S1 and S3).

- Home visits and telemedicine:

DCTs may help participants avoid travel and reduce the burden and costs of a face-to-face visit as explained above (see S3).

- Delivery of IMP

Where permitted, IMP is delivered directly to the participants' home or to a nearby location (to their health centre or the pharmacy in their neighbourhood), avoiding the burden of having to go to the site.

- Self-monitoring

This allows the participant greater autonomy, as activities can be included in their daily routine and often reduce the burden (e.g. with devices that continuously monitor blood glucose levels).

S7. Possibility to reach more geographically dispersed and diverse populations

With eConsent and screening via remote visits it is possible to achieve a more diverse population, reaching regional and remote areas and potentially including underrepresented populations, overcoming two of the main barriers to participation: the distance of the participant to the study site and taking the participant out of their normal environment.

S8. Potential improvement of participants' health and digital literacy skills

Low levels of health and digital literacy skills can be associated with poor access to health services and poor health status and can lead to a lack of understanding of basic health information for decision making.

Participation in DCTs can contribute to improving the health and digital literacy of

participants. The use of eConsent gives the possibility to include a glossary of terms or to use a layered approach that allows the participant to deepen the information he/she finds most relevant or to gain clarification on terms he/she does not understand. In addition, self-monitoring (which should be accompanied by training materials) allows participants to increase their skills with digital technologies (e.g. glucometer; blood pressure monitor) and participating in data generation and recording can lead to improved digital and health literacy.

As discussed in S4, this may help a participant with their decision making and may also result in the participant improving their autonomy and even improving their adherence to treatment after the clinical trial.

S9. Easier to detect external factors that would go unnoticed in visits performed on site

Remote screening and home health visits may include the possibility to collect information from the participants' environment that would not be captured on site, detect ancillary care obligations and other external factors that would not be registered during a clinic visit (extra need of care, risky environment for the participant, child abuse, etc.).

S10. Possibility of increasing the data collected for both research and safety monitoring

Remote monitoring systems can help to improve participant quality of life, decreasing unscheduled visits and reducing the use of health resources. Also, devices allow data to be collected (sometimes continuously) and sent remotely to the research team; this strategy makes it possible to prevent or detect adverse events at an early stage and to react faster in case of safety issues.

Due to the continuous collection of constants and symptoms, the loss of data that would be collected in retrospective visits is avoided. The digitization of information facilitates the collection of data in a real-world context.

S11. Easier to monitor/audit/inspect

The eConsent facilitates the storage and management of documentation, including the different versions of the informed consent used and signed during the trial in digital format. This allows clinical research assistants and auditors to review them remotely in an easier way. The same applies to digital data regarding key measurements and endpoints that are

collected on an on-going basis digitally.

A3.2.2. Weaknesses

W1. Barriers due to the use of digital technologies

The use of digital technologies in DCTs can lead to barriers of different nature, including:

- Exclusion of participants

In DCTs, on the one hand, specialist equipment is required to enable remote participation (e.g., internet connection, electronic devices, contracted energy power) and on the other hand, knowledge to carry out the required procedures/practices. These criteria can lead to an exclusion of certain individuals or even social groups (e.g., communities with low internet coverage, poor technical skills or lack of own devices such as smartphone or tablet).

- Decrease of quality of data

The use of mobile devices for self-monitoring may cause participants to measure constants incorrectly and the data obtained may not be accurate due to human error, such as unfamiliarity with the devices (leading to wrong measurements); or due to technical errors, such as failures of the device itself (e.g. lack of connection). In some cases, it may also be difficult to identify device failures, resulting in erroneous data.

Lack of experience, Standard Operating Procedures (SOPs), and inadequate guidelines in this type of trial may also result in lower quality of data.

- Costs linked to the implementation/use of these technologies

The use of technologies and electronic devices in DCTs entails a cost that must be borne by both the sponsor and the participant. In addition to the cost of the devices, there is the cost of the development of suitable applications (apps) or electronic consents used during the trial.

On the participant's side, the use of these devices may entail associated costs, such as electricity consumption or internet connection, which should be compensated (refunded).

- Focus on digital materials during the consent process

Besides the aforementioned cost of development, the use of eConsent carries certain risks, such as focusing consent only on digital materials and de-emphasising the importance of the discussion with the research team, missing relevant information for the potential participant (e.g., in the layered approach) or the lack of paper backups.

- Impact of external elements

As mentioned above, during the visits there may be external elements that we cannot control (noise environment that makes difficult to interview, internet outages or/and device connectivity failures that make consultation difficult, etc.).

W2. Lack of face-to-face (on-site) contact

Traditionally, medicine has been based on the individual relationship between patient and doctor. The lack of face-to-face visits can make it more difficult to build a relationship of trust between researcher and participant, as often visits via a device can make it more difficult to achieve a relationship of trust that allows concerns to be shared.

In addition, with the lack of physical examinations and absence of non-verbal information, it can be difficult to verify underlying conditions, check understanding or verify voluntary consent.

In the context of telemedicine, it can be more difficult to verify the presence of other people in the conversation (people not appearing on camera).

W3. Difficulties to verify the identity

DCTs involve a strong awareness of the importance for authentication and verification of the identity of both the participants and the research team to ensure that privacy is maintained and that third parties do not access the information and data generated. Verification is not only important in the case of informed consent or telemedicine visits, but also in the case of self-monitoring, as the data collected using the devices must be only from the participant and no one else should collect data using the device (e.g., if it is a glucometer, the participant's partner may use it to check their blood glucose level on a particular day, if this data were transferred, it would be erroneous data and could compromise the quality of the data).

W4. Privacy issues

- Regulations

Maintaining privacy during DCTs is vital to the smooth running of the study, therefore it is important to ensure that existing regulations provide strong and secure privacy for participants. Many current applications, such as video calling, recording physical activity, or managing a messaging service, may not meet the security and privacy requirements for this type of study and may request permissions that are unnecessary for their function.

- Access to data by third parties

The software used during the clinical trial must have all the guarantees of data protection.

Data collected by devices or using apps will often also be processed by third parties, which will usually serve in a vendor role, but sometimes also under the wings of the sponsor. These roles may sometimes be unclear, especially to participants, and this lack of clarity can also give rise to security and control issues, e.g. third parties exploiting data gathered in the context of the trial for their own purposes without participants explicitly consenting to this. The role of third parties (e.g., for Investigational Medicinal Product (IMP), if an external company is used for transport, the participants' data is shared with a subcontractor) should be carefully considered from an ethical and privacy as well as from a Good Clinical Practice (GCP) perspective. Lack of experience with remote visits, highlights the need for clear SOPs.

Recordings made and written conversations should only be accessed by those delegated to do so and cannot be stored or reviewed by third parties or vendors.

Participants may feel that they are not in control of their own data. In the ICF, it should be stated who will have access to their data, where it will be stored, for how long, etc.

- Risk of perceived invasiveness

Home health visits may be invasive for some participants, or they may not be comfortable with receiving people in their home (because their home is not as tidy as they would like it to be, they may feel judged, it may create a stigma in their neighbourhood to see them receiving regular visits from health personnel, etc.).

Telemedicine visits can also be invasive for some participants. The device's camera only focuses on what the user wants to show. To maintain the anonymity and privacy of the participant, no one else should be in the room (although there may be third parties in the participant's room because he/she does not mind that they know that he/she is participating in a study or the activities he/she has to carry out, or they may have a caregiver role).

W5. Not suitable for all clinical trials, therapeutic areas, participants, and activities (remote data collection will not be feasible for all measurements)

DCTs are an operational strategy to enhance clinical trials, but they are not suitable or the best option for all therapeutic areas or target populations.

Beyond the inclusion and exclusion criteria, the choice to use this operational strategy also depends on the profile of the participants, where age, socio-economic status or digital and health skills may be a barrier to participation in some of these studies (as mentioned in W1). Aspects such as availability of electronic devices and internet connection or digital literacy might have to be taken into account in addition to the inclusion criteria.

The therapeutic area of the study is also an important factor when deciding whether to apply this operational strategy (e.g., infusion medicines that need real time blood monitoring may not be suitable for a DCT approach). Moreover, not all actions can be performed in home health visits; some tests may require the use of diagnostic devices that are only available in hospitals such as scanners for cancer studies.

W6. Increased burden and responsibility on participants to do some activities themselves

In DCTs, participants carry out some trial activities and record data themselves. Participants need to be trained and become accustomed with the use of the various technologies. This delegation of activities can lead to increased responsibilities, increased time spent on trial related activities and overall burden during the trial.

If the IMP is not administered correctly or data is not recorded well, this can lead to poor quality data and/or failure or delays in the detection of adverse effects (W1). Furthermore, there may be additional difficulties in managing complex or severe adverse events in a virtual trial setting.

W7. Difficulties for the participants to perform the activities themselves

In line with the previous item, some participants may have problems in carrying out activities on their own. They may not understand how to use the technology and devices correctly (see W1), leading to incorrect measurements and generating poor quality data (see W13). Other problems that may arise are difficulties in identifying faults in the devices or not knowing how to act in case of a problem with the devices, as well as not being able to detect possible adverse events as already mentioned above.

In DCTs, participants will need to be trained and become accustomed with the use of the technologies.

W8. More burden or risk-taking for the health care providers

The investigator team may also see their burden and risk-taking increase.

Increased training is required for various technologies, together with increased monitoring of the data. Continuous generation of data by participants must be reviewed for quality and possible adverse effects. In addition, the frequency of unscheduled telemedicine visits may increase.

Another problematic point is home health visits and the risk of contamination with disease: the participant's home environment cannot be controlled, the health worker may be at risk of disease contamination, and some tests may be problematic due to the risk of contamination of instruments and biosamples (see W10).

W9. Difficulties in the management and organization/configuration of the investigator team

The responsibility of the PI increases in DCTs, as there are more third parties to monitor and more people delegated for different activities, including home health visits.

Some PIs could prefer not to delegate these activities, especially home health visits, to the nurses or other members of the team.

Problems that may arise during management of the research team in DCT include: problems of supervision, due to third parties conducting the visits or activities (e.g. general practitioners or local laboratories); differences between countries in levels of nursing certification (not all nurses are trained to perform all procedures); or lack of experience in

decentralised trials, with a shortage of qualified health professionals who can conduct them.

W10. Difficulties in the management and conservation of the biosamples

Home health visits and self-sampling can complicate the management and preservation of biological samples. On the one hand, there is the risk of sample contamination in the participant's home environment, as it cannot be ensured that it is an aseptic environment during collection. During transport, samples may be damaged by various factors (temperature control, packaging, photosensitive samples, leakage, etc.), and there is the added requirement of having to attach all the necessary documentation to be able to trace the bio-sample.

W11. Difficulties in the management, conservation and administration of the IMP

IMP management operations present several challenges. Firstly, its handling and administration must comply with Good Distribution Practices (GDP) (temperature control, storage, etc.). Secondly, a correct transfer must be ensured until the delivery of the IMP to the participant (to avoid being received by third parties, comply with regulatory requirements, etc.).

When IMP is sent to the participant's home or environment, its control by the responsible pharmacist (safety and quality of the product) is lost. Incidents may appear during the transfer, for which a protocol must be established in order to cover this range of problems.

W12. Generation of unnecessary data for the research

Continuous monitoring of participants generates a large amount of data, some of which may be unnecessary, requiring resources and standardised procedures to review and analyse them properly (see W8 for the consequences of the increased burden on the research team).

W13. Risk of generating invalid data or with questionable quality

In the same way that a lot of data are generated (some of them unnecessary, see W12), there is also a risk of generating invalid data or data of questionable quality. Participants may be unfamiliar with the devices and equipment and therefore make incorrect

measurements. If the data are not well recorded, they may not be valid for the study.

W14. Dehumanisation of the participant

Technology might interfere with the relationship between the participant and the doctor.

The participant's experience may not be entirely pleasant because there is no face-to-face contact (see W2) and it is more difficult to build a relationship of trust through telemedicine visits. For many participants, physical contact is part of the overall healthcare encounter, and they may feel that remote visits do not lead to a complete and correct diagnosis.

It is sought to try to transfer to telemedicine visits the atmosphere that would be present in the consultation room.

A3.2.3. Opportunities

O1. Harmonisation in the regulation and legislation

For many of the DCT processes, there is now a great opportunity to evolve to a common legislation, both on the EU and the national level (e.g. electronic informed consent, acceptance of electronic signatures and ID verification).

Promoting the use and harmonising the regulation of decentralised processes at European level could have a positive impact on DCT acceptance, promote development of applications for these processes and facilitate the implementation of DCTs.

O2. Collaboration with local resources

Local resources (health centres, pharmacies, etc.) can offer an alternative to travelling to the research site, for example for physical examinations or the dispensing of certain medical products. To this end, it is important that communication and collaboration with these resources are established and enhanced, and that protocols are established to regulate the roles of these resources and professionals in the clinical trial. This collaboration may also allow to provide the participant with options to supplement the DCT processes.

A3.2.4. Threats

T1. Non harmonization of the legislation/acceptance on DCTs

Currently, there are legislative differences at national and international levels that affect several DCT processes. This is especially relevant for legislation on digital/electronic procedures. Legislative differences in e-signatures or telemedicine, for example, are some of the main handicaps for the effective development and implementation of DCTs.

This lack of legislative harmonisation is especially a barrier to the organisation of multinational trials at all levels: local, regional, national and European; because it impedes coordination between different authorities as well as between different research teams in each territorial jurisdiction.

This fragmentation also relates to data protection as some legislative elements (particularly for health data) are divergently arranged at the EU member state level (27).

GCP is currently undergoing a revision process. It is currently uncertain what specific standards will be introduced for DCTs but there is clearly growing interest in this area.

T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs

The absence of harmonised legislation can be an obstacle in the development of DCTs, affecting not only the assessment of such clinical trials from the regulators' point of view of but also the ethics committees.

The lack of harmonised regulation is aggravated by the lack of knowledge and experience accumulated in the development of DCTs, which could help to identify conflicting aspects or areas that need specific clarification in order to be assessed by ethics committees. In addition, lack of experience can lead to problems for researchers in dealing with unforeseen events, facing situations in the process itself or even after the process has been completed (e.g. what to do with the device once it is finished).

There is also a need for industry standards on how to deal responsibly with many of the technologies and services used in DCTs, in ways which allow respect for both GCP requirements (aimed at protecting confidentiality, but also data integrity etc.) and data

protection requirements (stressing the need for data minimisation etc.).

T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs).

As well as a lack of legislation (T1) for certain aspects of the use of technological tools on clinical trials, we find the other side of the coin in the over-regulation of more common aspects, such as the use of apps, sports watches or other devices by considering them as medical devices. The complexity in the regulation of these devices may also limit their implementation of DCTs, as the use of technologies and applications in DCTs is higher than in TCTs.

The fact that common tools used in DCTs have more restrictive regulations than those not intended for health or research uses leads to a greater administrative burden that hinders or delays the implementation of these trials.

At the very least, DCTs face a complex, burdensome, and fragmented regulatory environment with reference to the technologies being used for measurements. This applies to the selection and admission of tech used: blurring of the lines between health consumer apps and tech and medical devices, approval processes for medical devices, intended vs non-intended use. It also applies to the admission of data and evidence garnered in this way: e.g. approval trajectories for digital endpoints, Health Technology Assessment (HTA).

T4. Professional certifications and qualifications are not homogeneous among countries.

The lack of harmonisation of certificates and the competences assigned to them may pose a threat to the organisation of multi-country trials as there may be differences between certificates and their competences in countries where the trial takes place (e.g. who can perform blood sample or other biosample collection). In addition, this disparity of certifications can lead to misunderstandings when it comes to setting up the research teams and the appropriate profiles for each task.

A4. Conclusions

To summarise the SWOT, the use of remote, digital consent and digital technologies in clinical trials has a series of significant strengths, such as remote access, freer decision-making, ease of follow-up actions, and the possibility of reaching geographically dispersed

and diverse populations. However, there are also associated weaknesses and challenges, such as barriers related to the use of digital technologies, lack of face-to-face contact, difficulties in verifying identity, privacy issues, and the need to adapt procedures to different therapeutic areas and participants. To maximise the potential of decentralised clinical trials, it is necessary to address barriers, adapt to challenges, maintain positive aspects, and exploit identified opportunities. It is recommended to address barriers related to the adoption of digital technologies, provide adequate training and support to participants and healthcare professionals, implement robust identity verification methods, and maintain strong security and privacy measures. In addition, it is important to adapt communications and procedures to maintain effective interaction with participants, establish a robust and efficient management structure, take advantage of regulatory and legislative harmonisation efforts, and explore partnerships with local resources to facilitate the implementation of DCTs.

As shown, many more internal elements have been identified (11 strengths and 14 weaknesses) than external (2 opportunities and 4 challenges), and more aspects have been identified that hinder the implementation of DCTs (W and T) than facilitate them (S and O).

The greater number of internal (S and W) than external (O and T) aspects suggests that the differences between the procedures to be followed in traditional and decentralised CT strategies do have an impact on the ethical, legal, and regulatory aspects of CT. The existence of more constraints than facilitators shows on the one hand that DCTs is still in a definition/construction phase and on the other hand that fully DCT is not considered feasible in most cases and, at least for the time being, hybrid options should be used.

PART B- Identification of the main ethical, legal, and operational challenges for DCT in the EU

B1. Objective and Methods

B1.1 Objective

Identify the main ethical, legal, and operational challenges for DCTs in the EU.

B1.2 Methods

To identify the main challenges faced by the DCTs, a questionnaire was drawn up based on the results of the SWOT analysis, in which a panel of experts assessed the importance given to each item and, in the case of opportunities and threats, indicated the probability of their occurrence.

The expert panel was composed of members of the 2 advisory bodies of the Trials@Home project: the External Stakeholder Platform (ESP) and the diabetes Patient Expert Panel (PEP). The ESP is composed by members of the following stakeholders: patient organisations; healthcare providers; clinical research; pharma; medtech; technology; regulatory; HTA; payers; ethics. The PEP is composed by representatives of the community of people living with diabetes in Europe.

The process of requesting participation and communication with the panellists was carried out following the established process and through the contact persons stipulated by the project. Panellists received the survey with the descriptions of each item by mail and were given six weeks to respond to the survey. The survey was designed in RedCap® and was completed electronically by the panellists.

The results have been analysed on the one hand with the total sample and on the other hand with only the members of each advisory group. The latter analysis is due to the difference in profile composition between the two advisory groups, since while the ESP has a diverse sample of different stakeholders, the PEP consists of people with lived experience of diabetes (people living with diabetes as well as carers/parents). This difference between the two groups was taken into account when selecting the items that are considered to be the main challenges of the DCTs; in general, the results of the ESP have been prioritised as they present a more diverse sample, and the different stakeholders are represented.

Following internal discussions in several meetings, the members of the D4.2 working group decided to consider the following criteria for the selection of the SWOT analysis items that represent the main ethical, legal and operational challenges for DCTs in the EU:

Criterion 1: The weaknesses, opportunities and threats considered important by the ESP.

Criterion 2: The weaknesses, opportunities and threats considered most important (with higher median and mean) by the PEP.

Criterion 3: The threat considered most likely to occur (and with high or medium importance).

Criterion 4: There should be at least one item from each of the components of the SWOT analysis, except for strengths, which have been excluded as they are not considered as challenges.

B1.2.1. Criteria for the assessment of the importance of the SWOT items[1]

- Strengths and weaknesses

Importance levels were determined by the median of the panel and the presence (or absence) of disagreement. Median ratings falling exactly between the 3-point boundaries (3.5 and 6.5) have been included in the extreme categories.

Degree of importance:

"Important" or "critical": panel median of 6.5–9 (Important: 6.5 -7.5; Critical: 8 – 9), without disagreement.

"Moderate": panel median of 3–6 or any median with disagreement.

"Trivial" or "Acceptable": panel median of 1–3.5 (Trivial: 1-2; Acceptable: 2.5-3.5), without disagreement.

The definition of disagreement depends on the panel size and the distribution of the panellist ratings on the 3-point regions (1-3: Low importance; 4-6: Medium importance; 7-9:

[1] Methodology based on the RAND/UCLA Appropriateness Method User's Manual

High importance). As there were “I Don’t know” and “No opinion” categories of response, the panel size was calculated for each recommendation including only responses with a rating of 1–9. So, we considered that there was "Disagreement" when the number of panellists rating in each extreme (1-3 and 7-9) is at least 3 (when 8 to 10 panellists rank importance) or 4 (when 11 to 13 panellists rank importance).

Importance (Median)

1 – 2 without disagreement	2.5 - 3.5 without disagreement	4 – 6 or any median with disagreement	6.5 - 7.5 without disagreement	8 – 9 without disagreement
Trivial	**Acceptable**	**Moderate**	**Important**	**Critical**

Figure 3. Categories for the identification of the importance of the elements identified in SWOT

- *Opportunities and threats*

Importance levels were determined by the median of the panel, the presence (or absence) of agreement and the possibility considered by the panel to occur. Median ratings falling exactly between the 3-point boundaries (3.5 and 6.5) have been included in the extreme categories.

Degree of importance:

“*High*”: panel median of 6.5–9, without disagreement.
“*Medium*”: panel median of 3–6 or any median with disagreement.
“*Low*”: panel median of 1–3.5, without disagreement.

The definition of disagreement follows the same criteria as for the strengths and weaknesses.

The classification of the item as “Trivial”; “Acceptable”; “Moderate”; “Important” or “Critical” depended on the importance and the probability of occurrence (most voted category of response excluding “I don’t know”) as indicates the following table:

	Importance (median)		
Probability to occur (most voted category)	*Low* (1-3.5 without disagreement)	*Medium* (4 – 6 or any median with disagreement)	*High* (6.5 - 9 without disagreement)
Low	**Trivial**	**Acceptable**	**Moderate**
Medium	**Acceptable**	**Moderate**	**Important**
High	**Moderate**	**Important**	**Critical**

Figure 4. Categories for the identification of the importance and probability of the elements identified in SWOT

B2. Results

	ESP		**PEP**		**ESP + PEP**	
Advisory Group	**n**	**%**	**n**	**%**	**n**	**%**
PEP	0	0%	7	100%	7	54%
ESP	6	100%	0	0%	6	46%
Area of expertise (Multiple response)	**n**	**%**	**n**	**%**	**n**	**%**
Ethical aspects	0	0%	0	0%	2	15%
Legal aspects	0	0%	0	0%	1	8%
Regulatory aspects	2	33%	2	33%	3	23%
Clinical Trials	4	67%	4	67%	5	38%
Patient engagement	2	33%	2	33%	9	69%
Other	3	50%	3	50%	3	23%

Figure 5. Distribution of panellists according to area of expertise and advisory group to which they belong

B.2.1. Results of the assessment of the importance given to each item of the SWOT analysis:

STRENGTHS	**ESP**	**PEP**	**ESP + PEP**
S1. Potential benefits of using eConsent			
S2. Potential benefits of using digital technologies for other study procedures different to eConsent			
S3. Remote access			
S4. Increased/enhanced free decision making			

S5. Easier to carry out follow-up actions			
S6. Less burden for participants			
S7. Possibility to reach more geographically dispersed and diverse populations			
S8. Potential improvement of participants' health and digital literacy skills			
S9. Easier to detect external factors that would go unnoticed in visits performed on site			
S10. Possibility of increasing the data collected for both research and safety monitoring			
S11. Easier to monitor/audit/inspect			

WEAKNESSES	ESP	PEP	ESP + PEP
W1. Barriers due to the use of digital technologies			
W2. Lack of face-to-face (on-site) contact			
W3. Difficulties to verify the identity			
W4. Privacy issues			
W5. Not suitable for all clinical trials, therapeutic areas, participants, and activities (remote data collection will not be feasible for all measurements)			
W6. Increased burden and responsibility on participants to do some activities themselves			
W7. Difficulties for the participants to perform the activities themselves			
W8. More burden or risk-taking for the health care providers			
W9. Difficulties in the management and organization/configuration of the investigator team			
W10. Difficulties in the management and conservation of the biosamples			
W11. Difficulties in the management, conservation and administration of the IMP			
W12. Generation of unnecessary data for the research			
W13. Risk of generating invalid data or with questionable quality			
W14. Dehumanisation of the participant			

OPPORTUNITIES	ESP	PEP	ESP + PEP
O1. Harmonisation in the regulation and legislation			

O2. Collaboration with local resources			
THREATS	**ESP**	**PEP**	**ESP + PEP**
T1. Non harmonization of the legislation/acceptance on DCTs			
T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs			
T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs)			
T4. Professional certifications and qualifications are not homogeneous among countries.			

The detailed results of the assessment of the importance given by the panellists to each element of the SWOT analysis are included in Annex 1.

B3. Conclusion

Different response trends were observed between ESP and PEP members. In general, the importance given by PEP members to weaknesses and threats are higher than by ESP members who, in the case of weaknesses, attach importance mainly to more logistical issues related to the collection, delivery and preservation of IMP and samples; aspects to which PEP members attach less importance.

In terms of identifying the main ethical, legal, and operational challenges for DCTs in the EU, the output of applying the criteria described in the methodology yielded the following results:

Criterion 1. *All weaknesses, opportunities, and threats considered important by the ESP.*

Weaknesses:

W8. More burden or risk-taking for the health care providers

W10. Difficulties in the management and conservation of the biosamples

W11. Difficulties in the management, conservation, and administration of the IMP

Opportunities:

O1. Harmonisation in the regulation and legislation

O2. Collaboration with local resources

Threats:

T1. Non harmonization of the legislation/acceptance on DCTs

Criterion 2. *The weaknesses, opportunities, and threats considered most important (with higher median and mean) by the PEP.*

Weaknesses:

W1. Barriers due to the use of digital technologies

Opportunities:

O1. Harmonisation in the regulation and legislation

Threats:

T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices).

Criterion 3. *The threat considered most likely to occur (and with high or medium importance).*

Threats:

T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs

Criterion 4. *There should be at least one item from each of the components of the SWOT analysis, except for strengths, which have been excluded.*

In view of the results obtained, this condition is fulfilled.

B3.1 Description of the main ethical, legal, and operational challenges for DCTs in the EU

Once the items to which the panellists gave the greatest importance were identified and the criteria defined in the methodology for defining the challenges were applied, the following 6 challenges were drafted and described/contextualised:

Challenge 1. *Decentralised clinical trials may increase the burden or risk-taking for the health care providers.*

In decentralised clinical trials, the research team may see an increase to their burden (e.g. increased training required for various technologies, increased monitoring activities) and risk-taking (e.g. risk of exposure to disease in an uncontrolled home environment).

Also, continuous generation of data by participants must be frequently reviewed to ensure data quality and to identify possible adverse effects.

In addition, the frequency of unscheduled telemedicine visits may increase.

Challenge 2. *Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples*

• Difficulties in the management, conservation, and administration of the IMP

The logistics of delivering the IMP to the participant may present several challenges in a DCT setting. Firstly, its handling must comply with Good Distribution Practices (GDP) (temperature control, storage, maintaining quality through the supply chain). Secondly, a correct transfer must be ensured until the delivery of the IMP to the participant (to avoid being received by third parties, comply with regulatory requirements, etc.) and once under control of the participant the IMP must be stored, handled, and administered appropriately. Additionally, when the IMP is sent to the participant's home or environment, its control by the responsible pharmacist may be altered and incidents may appear during the transfer, given the number of different possibilities of shipment in a DCT setting (e.g. from a clinical site or hospital pharmacy to participant, or from a local pharmacy to participant).

• Difficulties in the management and conservation of the biosamples

Home health visits and self-sampling can complicate the management and preservation of biological samples. On the one hand, there is the risk of sample contamination in the participant's home environment, as it cannot be ensured that samples were collected in an appropriate manner. On the other hand, during transport, samples may be damaged by various factors (temperature control, packaging, photosensitive samples, leakage, etc.), and there is the added difficulty of having to attach all the necessary documentation to be able to trace the biosample.

Challenge 3. Ensuring effective collaboration with local resources

Local resources (health centres, pharmacies, etc.) can offer an alternative to travelling to the research site, for example for physical examinations or the dispensing of certain medical products. To this end, it is important that communication and collaboration with these resources is established and enhanced; that protocols are established to regulate the

roles of these resources and professionals involved in the clinical trial; and to ensure appropriate training as required. This collaboration may also allow to provide the participant with options other than a fully DCT, however, this may add a burden of responsibility and increased workload to local resources.

Challenge 4. *Lack of harmonisation in the regulation and legislation*

Currently there are legislative differences at national and international levels that affect several DCT processes. This is especially relevant for legislation on digital/electronic procedures and on Direct to Participant IMP shipment.

Legislative differences in e-signatures or telemedicine are additional examples of the challenges for the effective development and implementation of DCTs.

This fragmentation also relates to data protection: some legislative elements of data protection, particularly for health data, are divergently arranged at the EU member state level.

This lack of legislative harmonisation is especially a barrier to the organisation of multinational DCTs at all levels because it impedes coordination between different authorities as well as between different research teams in each territorial jurisdiction. ICH E6 is currently undergoing a revision process. It is currently uncertain what specific standards will be introduced for DCTs.

Challenge 5. *Improving on the lack of specific knowledge and accumulated experience for ethical, legal and regulatory assessment of DCTs*

The absence of harmonised legislation and the lack of experience with evaluating full DCTs may affect the assessment of such clinical trials from the point of view of ethics committees and regulatory bodies.

The lack of harmonised regulation is aggravated by the lack of knowledge and experience accumulated in the development of DCTs to identify conflicting aspects or aspects that need specific clarification in order to be assessed by ethics committees. In addition, lack of experience can lead to problems for researchers in dealing with unforeseen events, facing situations in the process itself or even after the process has been completed (e.g. what to do with the device once the trial is completed).

There is also a need for industry standards on how to deal responsibly with many of the technologies and services used in DCTs, in ways that align with both GCP requirements (aimed at protecting confidentiality, but also data integrity, etc.) and data protection requirements (stressing the need for data minimisation, etc.).

Challenge 6. *Overcoming barriers due to the use of digital health technologies*

The use of digital health technologies in DCTs can lead to barriers of different nature, including:

- Exclusion of participants. In DCTs, on the one hand, equipment is required to enable remote participation (e.g. internet connection, electronic devices, contracted energy power) and on the other hand, knowledge to carry out the required practices. These criteria can lead to an exclusion of certain individuals or even social groups (e.g. communities with low internet coverage or poor technical skills).

- Decrease of quality of data. The use of mobile devices for self-monitoring may cause participants to measure constants incorrectly and the data obtained may not be accurate due to human error, such as unfamiliarity with the devices (leading to wrong measurements); or due to technical errors, such as failures of the device itself (e.g. lack of connection). In some cases, it may also be difficult to identify device failures, resulting in erroneous data.

- Lack of experience, SOPs, and inadequate guidelines in this type of trial may also result in lower quality of data.

- Costs linked to the implementation/use of these technologies. The use of technologies and electronic devices in DCTs entails a cost that must be borne by both the sponsor and the participant. In addition to the cost of the devices, there is the cost of the development of apps or electronic consents used during the trial.

- On the participant's side, the use of these devices may entail associated costs, such as electricity consumption or internet connection, which should be compensated (refunded).

- Focus on digital materials during the consent process. Besides the aforementioned cost of development, the use of eConsent carries certain risks, such as focusing

consent only on digital materials and de-emphasising the importance of the discussion with the research team, missing relevant information for the potential participant (e.g. in the layered approach) or the lack of paper backups. In this respect it is worth mentioning that the EU recommendation paper of December 2022 encourages a virtual real-time face-to-face discussion.

- Impact of external elements. As mentioned above, during the visits there may be external elements that we cannot control (noise environment that makes difficult to interview, internet outages or/and device connectivity failures that make consultation difficult, etc.).

PART C- Possible solutions to ethical, legal, regulatory, and operational challenges for DCT in the EU

C1. Objectives:

This task has two main objectives:

1. Identify possible solutions to challenges.

2. Assess the appropriateness of these solutions.

C2. Methods

To achieve these two objectives, a Delphi methodology was used.

The Delphi method is a technique used to obtain consensus proposals from a group of experts on a specific topic. The process consists of conducting a series of surveys with participants who are experts in a variety of fields related to the topic. After each round, feedback is provided to the participants, allowing them to adjust their answers based on the responses of the other participants. This iterative process continues until the desired level of consensus is reached. In our case only two rounds were required, a first round in which experts generated proposals to address the challenges presented and a second round in which experts rated them on how effective they believed each proposal would be in addressing the identified challenges.

C2.1. Selection of experts

Based on the challenges identified in Part B, the professional profiles and areas of knowledge required to participate in the Delphi study were selected to generate proposals with which to address the identified challenges (round 1) and to evaluate (or rank) the proposals generated (round 2). From this exercise, 5 profiles and 5 areas of expertise were selected as follows:

- Professional profiles/stakeholders:
    - Patients
    - Researchers
    - Experts in ethics
    - Sponsors

- Regulators and experts in legislation

- Areas of expertise:

  - Clinical trials
  - Patient engagement
  - Ethical aspects
  - Regulatory aspects
  - Legal aspects

Once the type of professional profile and area of expertise were defined, the strategy for recruiting experts and the criteria to be considered as such were decided upon:

- Criteria for being considered an expert: Using the definition of Kennedy and Price, quoted in Yañez et al. (26), those who can make relevant contributions, given their knowledge or experience were considered experts. In this case we considered that the capacity to make relevant contribution could come from:

  - Years of experience in the field.
  - Publications on the subject matter.
  - Experience in having been involved in DCT (patient, investigator, sponsor) or in its regulation.
  - Being considered as an expert by others (snowball).

- Sampling strategy was a combination of:
  - Direct e-mail contact with experts found in the literature or as members of specialised groups (e.g. EFPIA DCT sub team).
  - Direct contacts in & through T@H contacts
  - Snowballing

C2.2 Description of the Delphi rounds:

Each round of the Delphi study corresponds with one of the objectives of this task.

C2.2.1. Round 1: Identification of possible solutions to challenges:

The aim of the first round of the Delphi study was to present 6 challenges to the panellists and collect their proposals on how to overcome them. A survey was prepared on the

RedCap® platform in which each of the challenges was explained and contextualised and an open question was included to ask for proposals on how to overcome each specific challenge. Information on the professional profile and expertise of the panellist was requested through multiple response questions.

The invitation to participate was sent by e-mail together with an explanation of the study and a link to this first survey. Initially, a period of two weeks was given to respond, but this was extended to 4 weeks to obtain the desired number of responses.

C2.2.2. Round 2: Assessment of the appropriateness of these solutions:

The aim of this second round was for the panellists to evaluate the proposals made by the panellists themselves during round 1 and to rank them on a scale of 1 to 4, where 1 was "not at all appropriate" and 4 was "totally appropriate".

Given the large number of identified solutions obtained in round 1 (among the 39 panellists, nearly 300 possible solutions were proposed) and in order to make their evaluation feasible, the responses were categorised. The panellists were asked to evaluate each of the categories and some examples of individual responses were also included to enable panellists to have a deeper understanding of each of the categories if needed.

The transition from the proposals obtained in round 1 to the categories to be evaluated by the panellists in round 2 was done in 2 steps:

Step 1. Content analysis of the proposals to detect common themes and to detect duplicate proposals. ATLAS.ti 23 software was used to facilitate this task. Categories were created in order to unify similar proposals under a joint solution. In performing this categorisation, responses were discarded if, despite having a valid entry, they did not provide a solution but were simply a comment or clarification to the proposed challenge.

Step 2. The categorized solutions/ proposals were presented to and discussed within the deliverable 4.2 working group during the Semi-Annual Meeting (SAM) held in Valencia in March 2023 to come up with a final categorisation.

Finally, the survey to be used in the second round of the Delphi study was created with RedCap® and sent to the panellists by email.

The survey was divided into six challenges with possible solutions within each section which the panellists were asked to rate the proposals on an appropriateness scale from 1 to 4. Appropriateness of the proposals was evaluated using the mean score and Bloom's cut-off point (quoted by Feleke, Wale and Yirsaw) (28). Bloom's highest category (in our case "Appropriate") is that whose mean score is above 80% of the maximum score; "Moderate" is that which is between 60 and 79% of the maximum score; and poor ("Not appropriate") is that whose mean score is below 60% of the maximum score.

	Not appropriate	***Moderate***	***Appropriate***
Mean	≤2.8	[2.8 - 3.4]	≥3.4

Figure 6. Criteria to indicate the relevance or otherwise of the proposals scored by the panellists in Delphi round 2

On the other hand, the criterion used to consider the existence of consensus, and thus when no further rounds of Delphi study assessment were necessary, was based on the proportion of panellists who were concentrated in each of the categories. Only 2 categories were considered: "Not appropriate" (scores 1 and 2) and "Appropriate" (scores 3 and 4). A sufficient degree of consensus was considered to exist when the proportion of panellists in one of the two categories was greater than or equal to 80% in at least 80% of the proposals evaluated.

C3. Results

C3.1. Results of Round 1:

To contact the panellists, more than a hundred emails were sent, from which 36 responses were obtained. Out of these 36, eight declined the invitation. The 28 that agreed to participate, were researchers (n=13), followed by sponsors (n=9), ethicist (n=8), regulator/legal experts (n=5) and patients (n=3). The areas of expertise included Ethical aspects (n=12), Legal aspects (n=3), Regulatory aspects (n=12), Clinical Trials (n=24) and Patient engagement (n=15). Of the 28 panellists, 23 stated that they had experience with DCTs and the rest stated that they had no experience with DCTs.

Of these 28 panellists, a total of 294 responses (i.e. potential solutions to the challenges) were obtained. After analysing and cleaning the responses (removing comments that did

not provide any proposals), the reference corpus was reduced from 294 to 259 responses. The 259 responses were eventually grouped into 39 examples across 6 categories (or challenges). These categories or challenges were presented in the survey (together with some examples) to allow panellists to assess them as potential solutions for each challenge. The categories and number of valid responses for each challenge are listed as follows and the process is summarised in Figure 7:

Challenge 1. *Decentralised clinical trials may increase the burden or risk-taking for the health care providers* =73.

Challenge 2. *Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples* = 59.

Challenge 3. *Ensuring effective collaboration with local resources* = 36.

Challenge 4. *Lack of harmonisation in the regulation and legislation* = 29.

Challenge 5. *Improving on the lack of specific knowledge and accumulated experience for ethical, legal and regulatory assessment of DCTs* = 40.

Challenge 6. *Overcoming barriers due to the use of digital technologies* = 57.

	Ch1	Ch2	Ch3	Ch4	Ch5	Ch6	Total
Initial responses (from Round 1)	73	59	36	29	40	57	294
Initial responses after removing those that were not solutions (ATLAS.ti)	64	47	34	23	37	54	259
Examples included per category (Challenge) in Round 2 for evaluation by panellists	9	7	5	6	4	8	39

Figure 7. Process of categorisation of the proposals for each challenge

To learn more about the composition of these solutions based on the panellists' responses, please refer to Annex 2.

C3.1.1. Categories (Challenges) for assessment by panellists during Round 2:

Challenge 1. *Decentralised clinical trials may increase the burden or risk-taking for the health care providers.*

The proposals identified to overcome this challenge were grouped by their similarity into the following 9:

- By paying more attention to trial safety conditions
- By developing and improving training and support
- By ensuring remote follow-up of the safety of participants
- By tailoring trial set-up to DCT elements
- Through development and selection of more adequate and standardised technology
- By improving collaboration and involvement of all parties involved in trial conduct
- Through the development of a risk mitigation/management plan by the sponsor
- By facilitating peer-to-peer support among participants.
- Through automation of trial procedures

Challenge 2. *Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples.*

The proposals identified to overcome this challenge were grouped by their similarity into the following 7:

- By developing training and providing support to participants regarding use of medication and collection of biosamples.
- By adapting the study protocol to the therapeutic area, participant characteristics and study procedures
- By facilitating IMP management and temperature control
- By facilitating biosample management tracking
- Training of professionals for the new roles and delegated tasks of the DCT
- Using local pharmacies, pick-up points, laboratories and healthcare centres
- Use of validated products and services

Challenge 3. *Ensuring effective collaboration with local resources.*

The proposals identified to overcome this challenge were grouped by their similarity into the following 5:

- By reducing administrative burdens
- By providing better training and financial resources for local healthcare professionals
- By providing better incentives and compensation for involvement of local resources in trials
- By describing clearly the roles and functions of local partners
- Making local health care providers (HCPs) and patients aware of the importance of research for patients

Challenge 4. Lack of harmonisation in the regulation and legislation.

The proposals identified to overcome this challenge were grouped by their similarity into the following 6:

- By developing guidelines and facilitate/stimulate? knowledge sharing among stakeholders in DCTs
- Through gradual implementation of DCT elements incorporating adaptations to the local or national specificities.
- Stimulating learning and harmonisation between EU member states / internationally
- By centralizing clinical trial ethics review at the EU level
- By using advanced and verifiable digital security
- Through specialisation in DCT roles.

Challenge 5. *Improving on the lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs.*

The proposals identified to overcome this challenge were grouped by their similarity into the following 4:

- Through general knowledge-sharing, education, and training for conducting DCTs
- By promoting harmonisation of guidelines at European level and continuous dialogue with regulatory agencies
- By building expertise on DCTs and move towards centralised decision making**.**
- By simplifying and optimizing technology to reduce complexity.

Challenge 6. *Overcoming barriers due to the use of digital technologies.*

The proposals identified to overcome this challenge were grouped by their similarity into the following 8:

- By developing and improving training and support for participants and caregivers
- By making sure sufficient financial and technological resources are available to

participants.

- By making on-site/offline alternatives to decentralised elements available.
- By simplifying and adapting technology for participants' ease of use
- By ensuring data quality of remote/digital technologies used in DCTs
- Through local resources involvement.
- By centralising the DCT elements used in a single vendor
- By ensuring that discussion between the researcher and the potential participant is maintained as part of the informed consent process.

C3.2. Results of Round 2:

The purpose of this second round was for the panellists to assess the proposals they made themselves during Round 1, using a scale from 1 to 4, where 1 represented "not at all appropriate" and 4 represented "totally appropriate".

Eighteen out of 27 panellists who participated in the first round also participated in the second round survey. Their self-reported expertise was distributed as follows: 7 in ethics, 6 in legal, 6 in regulatory aspects, 16 in clinical trials and 8 in patient engagement.

The ranking of proposed solutions to the respective challenges are presented below. The proposals with a higher mean score are ranked higher (see Annex 2 for more details on scoring).

Challenge 1. Decentralised clinical trials may increase the burden or risk-taking for the health care providers

Ranking	Proposal	Appropriate %	Mean
1	By developing and improving training and support.	100%	3.67
2	By tailoring trial set-up to DCT elements	100%	3.31
3	By improving collaboration and involvement of all parties involved in trial conduct	94%	3.24
4	Through development and selection of more adequate and standardised technology	100%	3.22
5	By ensuring remote follow-up of the safety of participants	89%	3.17
6	Through the development of a risk mitigation/management plan by the sponsor	82%	3.12
7	By paying more attention to trial safety conditions	83%	3.11
8	Through automation of trial procedures.	59%	2.88
9	By facilitating peer-to-peer support among participants	31%	2.19

Challenge 2. Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples

Ranking	Proposal	Appropriate %	Mean
1	Use of validated products and services	94%	3.59
2	By facilitating IMP management and temperature control	100%	3.39
3	By developing training and providing support to participants regarding use of medication and collection of biosamples	94%	3.33
4	By adapting the study protocol to the therapeutic area, participant characteristics and study procedures	94%	3.29
5	By facilitating biosample management tracking	94%	3.29
6	Training of professionals for the new roles and delegated tasks of the DCT	100%	3.28
7	Using local pharmacies, pick-up points, laboratories and healthcare centres	83%	3.22

Challenge 3. Ensuring effective collaboration with local resources

Ranking	Proposal	Appropriate %	Mean
1	Making local HCPs and patients aware of the importance of research for patients	100%	3.50
2	By reducing administrative burdens	94%	3.39
3	By providing better training and financial resources for local healthcare professionals	100%	3.39
4	By describing clearly the roles and functions of local partners	94%	3.39
5	By providing better incentives and compensation for involvement of local resources in trials	78%	3.17

Challenge 4. Lack of harmonisation in the regulation and legislation

Ranking	Proposal	Appropriate %	Mean
1	By developing guidelines and knowledge sharing among stakeholders in DCTs	100%	3.71
2	Stimulating learning and harmonisation between EU member states / internationally	100%	3.41

3	Through gradual implementation of DCT elements incorporating adaptations to the local or national specificities	100%	**3.40**
4	By using advanced and verifiable digital security	81%	**3.19**
5	Through specialisation in DCT roles	76%	**3.06**
6	By centralizing clinical trial ethics review at the EU level	59%	**2.76**

Challenge 5. Improving on the lack of specific knowledge and accumulated experience for ethical, legal and regulatory assessment of DCTs

Ranking	Proposal	Appropriate %	Mean
1	By promoting harmonisation of guidelines at European level and continuous dialogue with regulatory agencies	100%	**3.71**
2	Through general knowledge-sharing, education and training for conducting DCTs	88%	**3.47**
3	By simplifying and optimizing technology to reduce complexity	87%	**3.33**
4	By building expertise on DCTs and move towards centralised decision making	88%	**3.18**

Challenge 6. Overcoming barriers due to the use of digital technologies

Ranking	Proposal	Appropriate %	Mean
1	By developing and improving training and support for participants and caregivers	100%	**3.71**
2	By making sure sufficient financial and technological resources are available to participants	100%	**3.65**
3	By simplifying and adapting technology for participants' ease of use	100%	**3.53**
4	By ensuring that discussion between the researcher and the potential participant is maintained as part of the informed consent process	94%	**3.41**
5	By making on-site/offline alternatives to decentralised elements available	88%	**3.35**
6	By ensuring data quality of remote/digital technologies used in DCTs	94%	**3.31**

7	By centralising the DCT elements used in a single vendor	69%	**2.75**
8	Through local resources involvement	56%	**2.69**

Taking into account the percentage of consensus understood as the proportion of favoured responses (sum of the values 3 and 4 of the Likert scale, see Annex 3) over the total number of responses for that option, we can see that most of the proposals offered by the panellists in the first round reach a degree of consensus of over 80% (82% of the proposals obtain this classification, see Figure 8). This shows that the proposals are not polarised, which is why a third round of consultations was not necessary in this Delphi study.

Appropriate %	*n*	*Percentage*	*Cumulative percentage*
00%	**14**	**35.9%**	**35.9%**
>90%	**9**	**23.1%**	**59.0%**
>80%	**9**	**23.1%**	**82.1%**
<80%	**7**	**17.9%**	**100.00%**

Figure 8. Percentage of consensus (taking into account values 3 and 4 out of the total number of responses for each option) out of the total number of proposals.

C4. Conclusion

The study was conducted to identify and evaluate proposals to overcome six key challenges faced by DCTs. Common trends are evident for 3 challenges generated from the identified weaknesses, as well as for 2 challenges generated from threats (see section B of this deliverable). To address these challenges, the following solutions are proposed:

1. Regarding the 3 challenges referring to weaknesses the main solution identified is training and support for participants: It is essential to strengthen the health literacy and digital literacy of clinical trial participants through proper training, and adequate support should be provided throughout the clinical trial. This training and support should be provided by the research team and sponsors. It is important to avoid overburdening local HCPs by making them responsible for digital training when

digital components do not work or are not appropriate for the participant. It is also important to avoid entrusting the resolution of study participants' doubts to their peers.

2. Regarding the 2 challenges derived from identified threats, the best evaluated solution proposals have been the generation of clear and homogeneous guidelines, the creation of procedural guides and the sharing of expert knowledge. Proposals for centralisation of Research Ethics Committees (RECs) at the European level, have had a low acceptance.
3. In terms of proposals concerning opportunities, the importance of raising awareness among local HCPs of the importance and usefulness of research for their own patients stands out.

In summary, implementing these proposed solutions will contribute to addressing the identified challenges and improve the execution of DCTs, promoting more effective, ethical, and higher quality research.

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ANNEXES

Annex 1- Results of the assessment of the importance given by the panellists to each element of the SWOT analysis

External Stakeholder Platform (ESP)

Profile of panellists:

Area of expertise (Multiple response)	**n**	**%**
Ethical aspects	0	0%
Legal aspects	0	0%
Regulatory aspects	2	33%
Clinical Trials	4	67%
Patient engagement	2	33%
Other	3	50%

Results of each item:

STRENGTHS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials to be in facilitating or improving compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

S1. Potential benefits of using eConsent (format, accessibility, use of digital technologies...)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	2	2	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	33%
7-9	4	67%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.0	
Standard deviation	0.9	

S2. Potential benefits of using digital technologies for other study procedures different to eConsent (e.g. ePRO, real time monitoring of participants, early detection of AEs/SAEs,

etc.)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	0	2	3	1	0

Answers in each interval	n	%
1-3	0	0%
4-6	0	0%
7-9	6	100%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.8	
Standard deviation	0.8	

S3. Remote access										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	0	3	1	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	33%
7-9	4	67%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.25	
Standard deviation	1.2	

S4. Increased/enhanced free decision making										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	1	0	2	0	2	0

Answers in the interval	n	%
1-3	0	0%
4-6	2	33%
7-9	4	67%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		

Mean	6,8
Standard deviation	2,0

S5. Easier to carry out follow-up actions										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	0	3	0	2	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	17%
7-9	5	83%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.3	
Standard deviation	1.5	

S6. Less burden for participants										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	1	0	1	4	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	17%
7-9	5	83%
Criteria:		
Median	9	
Disagreement	No	
Other Basic statistics :		
Mean	8.3	
Standard deviation	1.2	

S7. Possibility to reach more geographically dispersed and diverse populations										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	0	1	1	4	0

Answers in each interval	n	%
1-3	0	8%
4-6	0	8%
7-9	6	85%
Criteria:		

Median	9
Disagreement	No
Other Basic statistics :	
Mean	8.5
Standard deviation	0.8

S8. Potential improvement of participants' health and digital literacy skills										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	1	1	0	0	0	0	3	0

Answers in each interval	n	%
1-3	2	33%
4-6	1	17%
7-9	3	50%
Criteria:		
Median	6.5	
Disagreement	Yes	
Other Basic statistics :		
Mean	6.0	
Standard deviation	3.3	

S9. Easier to detect external factors that would go unnoticed in visits performed on site										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	2	0	1	0	1	1	0

Answers in each interval	n	%
1-3	1	17%
4-6	3	50%
7-9	2	33%
Criteria:		
Median	5	
Disagreement	No	
Other Basic statistics :		
Mean	5.7	
Standard deviation	2.4	

S10. Possibility of increasing the data collected for both research and safety monitoring										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	1	1	2	0

Answers in each interval	n	%
1-3	0	0%

4-6	2	33%
7-9	4	67%
Criteria:		
Median	7.5	
Disagreement	No	
Other Basic statistics :		
Mean	7.5	
Standard deviation	1.4	

S11. Easier to monitor/audit/inspect										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	0	2	1	1	1

Answers in each interval	n	%
1-3	0	0%
4-6	1	20%
7-9	4	80%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.2	
Standard deviation	3.2	

WEAKNESSES:

Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials are in hindering or worsening compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

W1. Barriers due to the use of digital technologies										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	2	0	2	1	0	1	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	6	50%
7-9	5	17%
Criteria:		
Median	5	
Disagreement	No	
Other Basic statistics :		
Mean	5.0	

Standard deviation	1.9

W2. Lack of face-to-face (on-site) contact										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	1	1	1	1	0	0

Answers in each interval	n	%
1-3	1	17%
4-6	3	50%
7-9	2	33%
Criteria:		
Median	5.5	
Disagreement	No	
Other Basic statistics :		
Mean	5.5	
Standard deviation	1.9	

W3. Difficulties to verify the identity										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	1	0	0	1	1	1	1	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	2	33%
7-9	2	33%
Criteria:		
Median	5.5	
Disagreement	Yes	
Other Basic statistics :		
Mean	4.8	
Standard deviation	2.8	

W4. Privacy issues										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	1	1	0	1	0	2	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	2	33%
7-9	2	33%
Criteria:		
Median	5	

Disagreement	Yes
Other Basic statistics :	
Mean	5.0
Standard deviation	2.8

W5. Not suitable for all the clinical trials, therapeutic areas, participants and activities (remote data collection will not be feasible for all measurements)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	2	0	1	1	1	0

Answers in each interval	n	%
1-3	1	17%
4-6	2	33%
7-9	3	50%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	2.2	

W6. Increased burden and responsibility on participants to conduct some study procedures themselves										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	2	1	2	0	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	4	67%
7-9	2	33%
Criteria:		
Median	5.5	
Disagreement	No	
Other Basic statistics :		
Mean	5.7	
Standard deviation	1.2	

W7. Difficulties for the participant to do the activities him/herself										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	0	0	2	3	0	0	0	0

Answers in each interval	n	%

1-3	1	17%
4-6	5	83%
7-9	0	0%
Criteria:		
Median	5.5	
Disagreement	No	
Other Basic statistics :		
Mean	4.8	
Standard deviation	1.9	

W8. More burden or risk-taking for the health care providers										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	1	1	2	1	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	50%
7-9	3	50%
Criteria:		
Median	6.5	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	1.5	

W9. Difficulties in the management and organization/configuration of the investigator team										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	1	2	1	0	0	0	1	0

Answers in each interval	n	%
1-3	2	33%
4-6	3	50%
7-9	1	17%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.3	
Standard deviation	2.7	

W10. Difficulties in the management and conservation of the biosamples										
Value	1	2	3	4	5	6	7	8	9	DN/NO

n	1	0	0	0	0	2	1	2	0	0

Answers in each interval	n	%
1-3	1	17%
4-6	2	33%
7-9	3	50%
Criteria:		
Median	6.5	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.6	

W11. Difficulties in the management, conservation and administration of the IMP										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	0	1	1	2	0	0

Answers in each interval	n	%
1-3	1	17%
4-6	2	33%
7-9	3	50%
Criteria:		
Median	6.5	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.1	

W12. Generation of unnecessary data for the research										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	1	0	2	1	0	0	1	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	3	50%
7-9	1	17%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.0	
Standard deviation	2.4	

W13. Risk of generating invalid data or with questionable quality										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	3	0	0	0	1	1	1	0

Answers in each interval	n	%
1-3	3	50%
4-6	0	0%
7-9	3	50%
Criteria:		
Median	5	
Disagreement	Yes	
Other Basic statistics :		
Mean	5.5	
Standard deviation	2.8	

W14. Dehumanisation of the participant										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	2	1	1	0	1	1	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	2	33%
7-9	2	33%
Criteria:		
Median	4.5	
Disagreement	Yes	
Other Basic statistics :		
Mean	5.0	
Standard deviation	2.1	

OPPORTUNITIES:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in enhancing or facilitating the implementation of Decentralised Clinical Trials:

O1. Harmonisation of the regulation and legislation										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	1	0	2	1

Answers in each interval	n	%
1-3	0	0%

4-6	2	40%
7-9	3	60%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.4	
Standard deviation	3.3	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	2	33%	33%
Medium probability	3	50%	50%
High probability	1	17%	17%
I don't know	0	0%	

O2. Collaboration with local resources										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	0	1	1	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	17%
7-9	5	83%
Criteria:		
Median	8.5	
Disagreement	No	
Other Basic statistics :		
Mean	7.8	
Standard deviation	1.6	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	17%	17%
Medium probability	3	50%	50%
High probability	2	33%	33%
I don't know	0	0%	

THREATS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in limiting or hindering the implementation of Decentralised Clinical Trials:

T1. Non harmonization of the legislation/acceptance on DCTs

Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	0	3	1	0	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	4	67%
7-9	2	33%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.7	
Standard deviation	1.3	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	0	0%	0%
Medium probability	1	17%	17%
High probability	5	83%	83%
I don't know	0	0%	

T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	0	3	1	0	0	0

Answers in each interval	n	%
1-3	1	17%
4-6	4	67%
7-9	1	17%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	5.4	
Standard deviation	1.5	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	17%	17%
Medium probability	4	67%	67%
High probability	1	17%	17%
I don't know	0	0%	

T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	0	1	0	1	1	1

Answers in each interval	n	%
1-3	1	20%
4-6	2	40%
7-9	2	40%
Criteria:		
Median (High importance)	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	3.3	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	17%	17%
Medium probability	4	67%	67%
High probability	1	17%	17%
I don't know	0	0%	

T4. Professional certifications and qualifications are not homogeneous among countries.										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	1	2	1	0	1	0	0	0

Answers in each interval	n	%
1-3	2	33%
4-6	3	50%
7-9	1	17%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.0	
Standard deviation	2.0	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	2	33%	40%
Medium probability	2	33%	40%
High probability	1	17%	20%

I don't know	1	17%

Patient Expert Panel (PEP)

Profile of panellists:

Area of expertise (Multiple response)	n	%
Ethical aspects	0	0%
Legal aspects	0	0%
Regulatory aspects	2	33%
Clinical Trials	4	67%
Patient engagement	2	33%
Other	3	50%

Results of each item:

STRENGTHS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials to be in facilitating or improving compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

S1. Potential benefits of using eConsent (format, accessibility, use of digital technologies...)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	1	1	2	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	14%
7-9	6	86%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	8.0	
Standard deviation	1.2	

S2. Potential benefits of using digital technologies for other study procedures different to eConsent (e.g. ePRO, real time monitoring of participants, early detection of AEs/SAEs, etc.)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	1	1	4	1	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	14%
7-9	6	86%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.7	
Standard deviation	1.0	

S3. Remote access										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	0	0	0	2	4	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	0	0%
7-9	6	86%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	6.9	
Standard deviation	2.2	

S4. Increased/enhanced free decision making										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	0	0	0	3	2	1	0

Answers in the interval	n	%
1-3	1	14%
4-6	0	0%
7-9	6	86%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.9	
Standard deviation	2.3	

S5. Easier to carry out follow-up actions										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	2	0	3	1	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	43%
7-9	4	57%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.1	
Standard deviation	1.5	

S6. Less burden for participants										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	0	1	2	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	14%
7-9	6	86%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.9	
Standard deviation	1.5	

S7. Possibility to reach more geographically dispersed and diverse populations										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	0	0	0	1	0	5	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	1	14%
7-9	5	71%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		

Mean	6.7
Standard deviation	2.6

S8. Potential improvement of participants' health and digital literacy skills										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	1	2	2	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	29%
7-9	5	71%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.6	
Standard deviation	1.3	

S9. Easier to detect external factors that would go unnoticed in visits performed on site										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	1	2	1	1	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	43%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.7	
Standard deviation	1.5	

S10. Possibility of increasing the data collected for both research and safety monitoring										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	0	3	2	1	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	3	43%
7-9	3	43%
Criteria:		

Median	6
Disagreement	No
Other Basic statistics :	
Mean	6.1
Standard deviation	1.6

S11. Easier to monitor/audit/inspect										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	2	3	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	29%
7-9	5	71%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.1	
Standard deviation	0.9	

WEAKNESSES:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials are in hindering or worsening compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

W1. Barriers due to the use of digital technologies										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	1	1	1	1	2	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	43%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.9	
Standard deviation	2.0	

W2. Lack of face-to-face (on-site) contact										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	1	1	0	1	3	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	2	29%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.4	

W3. Difficulties to verify the identity										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	1	0	3	1	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	2	29%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	5.9	
Standard deviation	1.9	

W4. Privacy issues										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	0	2	1	1	2	0

Answers in each interval	n	%
1-3	1	14%
4-6	2	29%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		

Mean	6.9
Standard deviation	2.1

W5. Not suitable for all the clinical trials, therapeutic areas, participants and activities (remote data collection will not be feasible for all measurements)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	0	0	2	3	0	1	0

Answers in each interval	n	%
1-3	1	14%
4-6	2	29%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.3	
Standard deviation	2.1	

W6. Increased burden and responsibility on participants to conduct some study procedures themselves										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	2	3	1	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	43%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.6	
Standard deviation	1.0	

W7. Difficulties for the participant to do the activities him/herself										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	4	1	1	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	5	71%

7-9	2	29%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.3	
Standard deviation	1.0	

W8. More burden or risk-taking for the health care providers										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	1	1	3	1	0	0

Answers in each interval	n	%
1-3	1	14%
4-6	2	29%
7-9	4	57%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.1	
Standard deviation	1.7	

W9. Difficulties in the management and organization/configuration of the investigator team										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	1	2	1	0	0	0	1	0

Answers in each interval	n	%
1-3	3	43%
4-6	3	43%
7-9	1	14%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.4	
Standard deviation	1.8	

W10. Difficulties in the management and conservation of the biosamples										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	2	2	1	0	0

Answers in each interval	n	%
1-3	1	0%
4-6	2	57%
7-9	3	43%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.3	
Standard deviation	1.1	

W11. Difficulties in the management, conservation and administration of the IMP										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	2	2	0	0	1

Answers in each interval	n	%
1-3	0	0%
4-6	4	67%
7-9	2	33%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.4	

W12. Generation of unnecessary data for the research										
Value	1	2	3	4	5	6	7	8	9	DN/NO
0	1	1	1	0	1	1	1	0	1	0

Answers in each interval	n	%
1-3	2	33%
4-6	2	33%
7-9	2	33%
Criteria:		
Median	5	
Disagreement	Yes	
Other Basic statistics :		
Mean	5.0	
Standard deviation	2.9	

W13. Risk of generating invalid data or with questionable quality										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	2	0	1	2	1	0	1

Answers in each interval	n	%
1-3	0	0%
4-6	3	50%
7-9	3	50%
Criteria:		
Median	6.5	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.7	

W14. Dehumanisation of the participant										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	4	0	1	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	6	86%
7-9	1	14%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	1.0	

OPPORTUNITIES:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in enhancing or facilitating the implementation of Decentralised Clinical Trials:

O1. Harmonisation of the regulation and legislation										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	0	4	1	0	2

Answers in each interval	n	%
1-3	0	0%
4-6	0	0%

7-9	5	100%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.2	
Standard deviation	3.5	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	3	43%	60%
Medium probability	1	14%	20%
High probability	1	14%	20%
I don't know	2	29%	

O2. Collaboration with local resources										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	0	1	1	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	33%
7-9	4	67%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.8	
Standard deviation	2.8	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	14%	20%
Medium probability	0	0%	0%
High probability	4	57%	80%
I don't know	2	29%	

THREATS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in limiting or hindering the implementation of Decentralised Clinical Trials:

T1. Non harmonization of the legislation/acceptance on DCTs										
Value	1	2	3	4	5	6	7	8	9	DN/NO

n	0	0	0	1	2	0	1	1	0	2

Answers in each interval	n	%
1-3	0	0%
4-6	3	60%
7-9	2	40%
Criteria:		
Median	5	
Disagreement	No	
Other Basic statistics :		
Mean	5.7	
Standard deviation	3.1	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	0	0%	0%
Medium probability	2	29%	40%
High probability	3	43%	60%
I don't know	2	29%	

T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	0	2	3	0	2

Answers in each interval	n	%
1-3	0	0%
4-6	0	0%
7-9	5	100%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.7	
Standard deviation	3.7	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	0	0%	0%
Medium probability	3	43%	60%
High probability	2	29%	40%
I don't know	2	29%	

T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	0	0	3	0	1	2

Answers in each interval	n	%
1-3	1	20%
4-6	0	0%
7-9	4	80%
Criteria:		
Median (High importance)	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.7	
Standard deviation	3.7	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	0	0%	0%
Medium probability	1	14%	20%
High probability	4	57%	80%
I don't know	2	29%	

T4. Professional certifications and qualifications are not homogeneous among countries.										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	0	2	1	0	2

Answers in each interval	n	%
1-3	0	0%
4-6	2	40%
7-9	3	60%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.5	
Standard deviation	3.3	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	2	29%	40%
Medium probability	2	29%	40%
High probability	1	14%	20%

I don't know	2	29%

Both Advisory Groups (ESP + PEP)

STRENGTHS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials to be in facilitating or improving compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

S1. Potential benefits of using eConsent (format, accessibility, use of digital technologies...)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	3	3	4	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	3	23%
7-9	10	77%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.5	
Standard deviation	1.1	

S2. Potential benefits of using digital technologies for other study procedures different to eConsent (e.g. ePRO, real time monitoring of participants, early detection of AEs/SAEs, etc.)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	1	3	7	2	0

Answers in each interval	n	%
1-3	0	0%
4-6	1	8%
7-9	12	92%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.8	
Standard deviation	0.8	

S3. Remote access										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	0	0	2	2	7	1	0

Answers in each interval	n	%
1-3	1	8%
4-6	2	15%
7-9	10	77%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.2	
Standard deviation	1.8	

S4. Increased/enhanced free decision making										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	0	1	1	0	5	2	3	0

Answers in the interval	n	%
1-3	1	8%
4-6	2	15%
7-9	10	77%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.8	
Standard deviation	2.1	

S5. Easier to carry out follow-up actions										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	2	3	3	3	0

Answers in each interval	n	%
1-3	0	0%
4-6	4	31%
7-9	9	69%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		

Mean	7.2
Standard deviation	1.4

S6. Less burden for participants										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	1	1	3	7	0

Answers in each interval	n	%
1-3	0	0%
4-6	2	15%
7-9	11	85%
Criteria:		
Median	9	
Disagreement	No	
Other Basic statistics :		
Mean	8.1	
Standard deviation	1.3	

S7. Possibility to reach more geographically dispersed and diverse populations										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	0	0	0	1	1	6	4	0

Answers in each interval	n	%
1-3	1	8%
4-6	1	8%
7-9	11	85%
Criteria:		
Median	8	
Disagreement	No	
Other Basic statistics :		
Mean	7.5	
Standard deviation	2.1	

S8. Potential improvement of participants' health and digital literacy skills										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	1	1	0	2	1	2	5	0

Answers in each interval	n	%
1-3	2	15%
4-6	3	23%
7-9	8	62%
Criteria:		

Median	8
Disagreement	No
Other Basic statistics :	
Mean	6.8
Standard deviation	2.5

S9. Easier to detect external factors that would go unnoticed in visits performed on site										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	2	2	2	2	2	2	0

Answers in each interval	n	%
1-3	1	8%
4-6	6	46%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	2.0	

S10. Possibility of increasing the data collected for both research and safety monitoring										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	0	0	5	3	2	2	0

Answers in each interval	n	%
1-3	1	8%
4-6	5	38%
7-9	7	54%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.8	
Standard deviation	1.6	

S11. Easier to monitor/audit/inspect										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	1	2	4	4	1	1

Answers in each interval	n	%
1-3	0	0%

4-6	3	25%
7-9	9	75%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.2	
Standard deviation	2.3	

WEAKNESSES:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider the following aspects of Decentralised Clinical Trials are in hindering or worsening compliance with ethical, regulatory, and legal requirements compared to Traditional Clinical Trials:

W1. Barriers due to the use of digital technologies										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	2	1	3	2	1	2	2	0

Answers in each interval	n	%
1-3	2	15%
4-6	6	46%
7-9	5	38%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.1	

W2. Lack of face-to-face (on-site) contact										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	1	2	2	1	2	4	0	0

Answers in each interval	n	%
1-3	2	15%
4-6	5	38%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	5.8	

Standard deviation	2.1

W3. Difficulties to verify the identity										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	1	1	1	2	1	4	2	0	0

Answers in each interval	n	%
1-3	3	23%
4-6	4	31%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	5.4	
Standard deviation	2.3	

W4. Privacy issues										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	2	1	0	3	1	3	2	0

Answers in each interval	n	%
1-3	3	23%
4-6	4	31%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.5	

W5. Not suitable for all the clinical trials, therapeutic areas, participants and activities (remote data collection will not be feasible for all measurements)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	1	1	0	2	2	4	1	2	0

Answers in each interval	n	%
1-3	2	15%
4-6	4	31%
7-9	7	54%
Criteria:		

Median	7
Disagreement	No
Other Basic statistics :	
Mean	6.2
Standard deviation	2.1

W6. Increased burden and responsibility on participants to conduct some study procedures themselves										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	3	3	5	1	0	0

Answers in each interval	n	%
1-3	0	0%
4-6	7	54%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	1.1	

W7. Difficulties for the participant to do the activities him/herself										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	0	0	3	7	1	1	0	0

Answers in each interval	n	%
1-3	1	8%
4-6	10	77%
7-9	2	15%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	5.6	
Standard deviation	1.6	

W8. More burden or risk-taking for the health care providers										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	2	2	5	2	0	0

Answers in each interval	n	%

1-3	1	8%
4-6	5	38%
7-9	7	54%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	1.5	

W9. Difficulties in the management and organization/configuration of the investigator team										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	4	3	3	0	0	1	1	0

Answers in each interval	n	%
1-3	5	38%
4-6	6	46%
7-9	2	15%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.4	
Standard deviation	2.1	

W10. Difficulties in the management and conservation of the biosamples										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	0	0	2	4	3	3	0	0

Answers in each interval	n	%
1-3	1	8%
4-6	6	46%
7-9	6	46%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.2	
Standard deviation	1.9	

W11. Difficulties in the management, conservation and administration of the IMP										
Value	1	2	3	4	5	6	7	8	9	DN/NO

n	0	0	1	1	2	3	3	2	0	1

Answers in each interval	n	%
1-3	1	8%
4-6	6	50%
7-9	5	42%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.0	
Standard deviation	2.2	

W12. Generation of unnecessary data for the research										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	2	1	3	1	1	1	2	0	1

Answers in each interval	n	%
1-3	4	33%
4-6	5	42%
7-9	3	25%
Criteria:		
Median	4	
Disagreement	No	
Other Basic statistics :		
Mean	4.5	
Standard deviation	2.6	

W13. Risk of generating invalid data or with questionable quality										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	3	2	0	1	3	2	1	1

Answers in each interval	n	%
1-3	3	25%
4-6	3	25%
7-9	6	50%
Criteria:		
Median	6.5	
Disagreement	No	
Other Basic statistics :		
Mean	5.8	
Standard deviation	2.7	

W14. Dehumanisation of the participant										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	2	1	3	4	1	2	0	0

Answers in each interval	n	%
1-3	2	15%
4-6	8	62%
7-9	3	23%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	5.5	
Standard deviation	1.6	

OPPORTUNITIES:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in enhancing or facilitating the implementation of Decentralised Clinical Trials:

O1. Harmonisation of the regulation and legislation										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	0	2	5	1	2	3

Answers in each interval	n	%
1-3	0	0%
4-6	2	20%
7-9	8	80%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	7.3	
Standard deviation	3.3	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	5	38%	45%
Medium probability	4	31%	36%
High probability	2	15%	18%
I don't know	2	15%	

O2. Collaboration with local resources										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	0	2	1	3	3	3	1

Answers in each interval	n	%
1-3	0	0%
4-6	3	25%
7-9	9	75%
Criteria:		
Median	7.5	
Disagreement	No	
Other Basic statistics :		
Mean	7.3	
Standard deviation	2.5	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	2	15%	18%
Medium probability	3	23%	27%
High probability	6	46%	55%
I don't know	2	15%	

THREATS:
Please, indicate in a scale from 1 to 9, with 1 being extremely low and 9 being extremely high (1-3 Low; 4-6 Medium; 7-9 High), how important do you consider that the following ethical, regulatory and/or legal factors are in limiting or hindering the implementation of Decentralised Clinical Trials:

T1. Non harmonization of the legislation/acceptance on DCTs										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	0	1	2	4	1	2	1	2

Answers in each interval	n	%
1-3	0	0%
4-6	7	64%
7-9	4	36%
Criteria:		
Median	6	
Disagreement	No	
Other Basic statistics :		
Mean	6.3	
Standard deviation	2.8	

How likely is to occur?	n	%	% (Exc. “I don’t know”)

Low probability	0	0%	0%
Medium probability	3	23%	27%
High probability	8	62%	73%
I don't know	2	15%	

T2. Lack of specific knowledge and accumulated experience for ethical, legal, and regulatory assessment of DCTs										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	1	1	0	3	3	3	0	2

Answers in each interval	n	%
1-3	1	9%
4-6	4	36%
7-9	6	55%
Criteria:		
Median	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.3	
Standard deviation	2.8	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	8%	9%
Medium probability	7	54%	64%
High probability	3	23%	27%
I don't know	2	15%	

T3. Regulatory requirements due to the use of multiple medical devices in DCTs (such as applications and devices used in DCTs)										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	0	0	2	1	0	1	3	1	2	3

Answers in each interval	n	%
1-3	2	20%
4-6	2	20%
7-9	6	60%
Criteria:		
Median (High importance)	7	
Disagreement	No	
Other Basic statistics :		
Mean	6.4	
Standard deviation	3.4	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	1	8%	9%
Medium probability	5	38%	45%
High probability	5	38%	45%
I don't know	3	15%	

T4. Professional certifications and qualifications are not homogeneous among countries.										
Value	1	2	3	4	5	6	7	8	9	DN/NO
n	1	0	1	2	3	0	3	1	0	2

Answers in each interval	n	%
1-3	2	18%
4-6	5	45%
7-9	4	36%
Criteria:		
Median	5	
Disagreement	No	
Other Basic statistics :		
Mean	5.0	
Standard deviation	2.7	

How likely is to occur?	n	%	% (Exc. “I don’t know”)
Low probability	4	31%	40%
Medium probability	4	31%	40%
High probability	2	15%	20%
I don't know	3	23%	

Annex 2. Composition of the solutions given by the panellists to overcome the main challenges of DCTs.

Challenge 1. *Decentralised clinical trials may increase the burden or risk-taking for the health care providers.*

1.A. By paying more attention to trial safety conditions

- Provide researchers with a safety kit for home visits.
- Liability insurance policies for clinical trials should include legal coverage for all activities performed at the patient's home.
- Institutional review of risks and burdens.
- Involve the research team in the assessment of potential increased burden, training or risk of exposure and in the proposal of mitigation strategies.
- The sponsor should establish a procedure for managing the most common risks, and this training for investigators could be included in the study initiation visit.

1.B. By developing and improving training and support

- Explain to the research team the need for additional training in consideration of potential benefits of DCTs.
- Change management earlier in the process. Don't wait until the last minute to inform sites about the inclusion of DCT elements into a trial when it's new to them.
- Ensure early engagement with sites (already during site feasibility stage), and communicate which DCT elements will be used. Ensure that DCT provider provides adequate helpdesk support for sites and patients. Ensure that proper training material is generated.
- Trial sites/researches need to receive specific training on the decentralised aspects of the trial and the specific rules in place.
- Use of digital tools where beneficial (and it is expected that the use of such tools in many areas will increase). Trial sites/researchers need to be trained on these tools.
- Formal but short education for involved patients has to be established.
- Sufficient well-trained support staff.
- Involve study partners (for example spouse, family member or good friend) who can help the participant when problems come up during the trial. Also create a participant manual with FAQ's.
- Create clear manuals and training videos, so that the research team can always look back at the material and only study the technologies that they need at that time.
- A formal but short education can be done in different ways. Researchers have to find with tests the best form to do it.
- Increase training for patients.
- Ensure early engagement with sites (already during site feasibility stage), and communicate which DCT elements will be used. Ensure that DCT provider provides adequate helpdesk support for sites and patients. Ensure that proper training material is generated.
- The sponsor should establish a procedure for managing the most common risks, and this training for investigators could be included in the study initiation visits.
- Allocate human resources to support the follow-up of participants' responses.
- Support trial sites/researches with trained personnel (study nurses) for the specific additional burden of decentralised trials.
- Including in the staff a new professional profile expert in digital health and in data analysis.

1.C. By ensuring remote follow-up of the safety of participants

- Schedule the contact moments (phone calls/telemedicine) in advance, so that the participant and their partner know when to expect a call. They can save their questions for that contact moment, unless they are very urgent. Also, if data is not coming in, this can be discussed during these contact moments.
- If continuous monitoring were to be further developed in special files, it could be fully automated, i.e. receiving a warning that a device (e.g. measuring daily motor activity) is not being used this day, etc.
- Define in the Protocol requirements for data review and no site should be expected to review data in real time.
- Intensive programming in the data collection system is needed to identify adverse effects that require contact with the HCP or intervention. Alerts for those that require assessment or action would be sent to HCP/coordinators for review. The study coordinators cannot be expected to review all the data submitted in real-time and provide timely assessment.
- Build alerts into digital tools to reduce the amount of manual review that's required.
- Optimize technology to allow participant to indicate need for clinical consultation, and have method for triaging and organizing.
- Have a protocol for events or participant reporting to identify problems in real time and then escalate to clinical attention in organized manner.
- Access to remote investigator and site staff for unplanned safety assessments requires coordination of multiple schedules (investigator, site staff, patient). Scheduling issues with telemedicine interactions may pose a risk to the timeliness, completeness, and accuracy of participant safety event reports. Since the investigator and study team do not intend to replace the participant's usual medical care, the participant's personal HCP represents a potential resource for optimising safety information collection, mitigating the duration and severity of an adverse event, and keeping the participant's HCP apprised of changes in their health status.
- Focus on patient-reported outcomes, less on measurements.
- Regarding monitoring of the data, develop a data flow at an early stage of the trial, including roles and responsibilities (e.g. PI responsibilities versus Sponsor's Medical Monitor's responsibilities). Work with DCT vendor and data management to define thresholds for automated alerts to sites/Sponsor. Communicate and engage early with sites at an early stage regarding their role with regard to monitoring data collected via DCT elements.

1.D. By tailoring trial set-up to DCT elements

- Procedures should be simplified as much as possible, not collect variables that will later have no clinical interest.
- If within-home monitoring or data collection is absolutely needed, perhaps limit it to a subgroup of participants of particular interest or perhaps a random smaller sample. This would avoid safety risks to the study team by minimizing the number of participants required for direct contact.
- Establish as inclusion criteria for patients some minimum requirements related to the patient's home: communications, accessibility, environment, location, resources and means available at home (dispensing and storage of medication, waste collection, for example).

- Selection right trials for DCT, for example low intervention trials.
- Protocol needs to identify which visits could be home visits or site visits. As researchers, we need to discuss this issue with the Sponsor, previously to get the final version of protocol and, we need to explain this possibility to patients in the PIS. It's important to calculate the timings. Probably a questionnaire and sampling requires 20 minutes but, if we need to process the samples or check information in a eCRF, probably they need to hold 1 hour.
- Trial sites/researches need to be supported by qualified service providers that have experience in decentralised trials (e.g. CROs, courier service, IT...).

1.E. Through development and selection of more adequate and standardised technology

- Use of digital tools where beneficial (and it is expected that the use of such tools in many areas will increase). Trial sites/researchers need to be trained on these tools.
- The use of AI should be explored and used.
- Having expert societies identify devices or apps (e.g. for spirometry) that meet acceptable standards for measurement. And have those societies work with the device companies to improve the precision of the measurements. In this way, there may be fewer 'recommended' devices/apps that would be used across clinical trials in a particular therapeutic area and coordinators would not have to learn a new device/app for each clinical trial. And encourage pharma to stop using homegrown data collection programs and use other standardized data systems such as REDCap.
- Standardized platforms for data collection/entry.
- Improving/choosing adequate technology (wearables).
- Use more wearable/sensor technology to track real time continuous data.
- Also easy to use with "walk me" technology so as not to require significant training.
- Make the technologies as 'dummy proof' as possible, meaning that the majority of the tasks should be automated. Steps that can be automated should be automated, before the start of the trial, so that the research team has as little work as possible.
- Allow for systems to trigger actions to reduce delays in actioning issues (using ML or AI for example).
- We need to provide better technology solutions that can integrate with other solutions and reduce multiple logins, double data entry, etc.
- Use DCT elements from 1 DCT provider via one DCT platform, to avoid that sites and patients need to handle several login data.

1.F. By improving collaboration and involvement of all parties involved in trial conduct

- The investigator should be involved in the design of the study to identify risks from the outset.
- Involve the research team in the assessment of potential increased burden, training or risk of exposure and in the proposal of mitigation strategies.
- Involve sites and participants into trial design so that burden can be reviewed up front.
- Ensure early engagement with sites (already during site feasibility stage), and communicate which DCT elements will be used. Ensure that DCT provider provides adequate helpdesk support for sites and patients. Ensure that proper training material is generated.
- Ensure early engagement with sites (already during site feasibility stage), and

communicate which DCT elements will be used. Ensure that DCT provider provides adequate helpdesk support for sites and patients. Ensure that proper training material is generated.

- The specific roles and responsibilities of the sponsor, investigator, and any additional parties need to be clearly defined in writing and understood prior to the start of the trial.
- Regarding monitoring of the data, develop a data flow at an early stage of the trial, including roles and responsibilities (e.g. PI responsibilities versus Sponsor's Medical Monitor's responsibilities). Work with DCT vendor and data management to define thresholds for automated alerts to sites/Sponsor. Communicate and engage early with sites at an early stage regarding their role with regard to monitoring data collected via DCT elements.
- Support trial sites/researches with trained personnel (study nurses) for the specific additional burden of decentralised trials.

1.G. Through the development of a risk mitigation/management plan by the sponsor

- The sponsor should establish a procedure for managing the most common risks, and this training for investigators could be included in the study initiation visits.
- Ensure that a thorough risk/benefit assessment is included in the protocol to ensure that it's assessed early and accepted by regulators - This should give confidence to sites and participants regarding the inclusion of DCT elements into a trial.
- Create a Risk mitigation/management plan which can be shared with sites to provide guidance on how to proactively manage potential or experienced issues.

1.H. By facilitating peer-to-peer support among participants.

- Peer to peer support may reduce fears and by that, also potential visits.

1.I. Through automation of trial procedures

- Data quality review is important, but increasingly becoming automated.
- Create automatic reminders for the research team when no data or bad quality data is coming in for a longer period of time. So change the activity of data monitoring to a passive instead of an active task.
- Allow for systems to trigger actions to reduce delays in actioning issues (using ML or AI for example).
- Regarding monitoring of the data, develop a data flow at an early stage of the trial, including roles and responsibilities. (e.g. PI responsibilities versus Sponsor's Medical Monitor's responsibilities). Work with DCT vendor and data management to define thresholds for automated alerts to sites/Sponsor. Communicate and engage early with sites at an early stage regarding their role with regard to monitoring data collected via DCT elements.

Challenge 2. *Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples.*

2.A. By developing training and providing support to participants regarding use of medication and collection of biosamples.

- Provide patients' homes with the necessary resources.
- Depending on the characteristics of the drug, send home the specific dose for each visit.
- Telephone support from participants.
- Scheduling telehealth calls to demonstrate appropriate collection technique and review by the packing materials for specimen shipment.
- Continuous follow up in courier web page for potential delays/issues in collection / shipments.
- The use of an app can help with biosampling at home. It can contain step by step guidelines for the sample collection, and literally walk them through it with diagrams, videos etc.
- Simplify study kits for participants to easily collect, store and ship samples.
- Include an adequate training for participants.
- Ensure training is provided and then people properly understand requirements and their importance.
- Training of participants in the use of medications and handling of specimens.
- For biosampling, involvement of Home Health Nurses or Televisits with the site's study team/study nurse who can instruct the patient remotely.
- Related to the management of biosamples an adequate information and training must be provided to the patient and, if it is necessary, a health-care professional must go to the patient's home to assist it.
- Provide participants with training on IMP management.
- Regarding IMP delivery to patient's homes (if allowed by local regulations and assuming that qualified vendors are used), suggest to involve Home Health Nurses or Televisits with the sites, to have a contact with the patient regarding the confirmation of correct delivery, and giving instructions regarding IMP storage and intake.
- Contracting with overnight delivery services with commitments for facilitating such work.
- Confirm with the participant the day and time to receive a drug / send an IMPs or biosample.

2.B. By adapting the study protocol to the therapeutic area, participant characteristics and study procedures

- Tailor research protocol according to participants / group of participants.
- Regarding drug, it depends on the trials. Sometimes you can give kits in the face-to-face visits at site.
- Chose or develop IMP that do not suffer from those problems
- The investigator could conduct home study feasibility surveys with candidates.
- Don't allow lab sample collections in the home for sensitive assays
- We need to detail all the procedures of the visit and which biological markers we need to analyse after sampling. Following the lab manuals we can assess the risks about the conditions accepted. This home visits modality is not available for all clinical trials and for all visits. If we need a refrigerated centrifuge immediately after the blood sampling, it could be difficult to perform at home (a refrigerated centrifuge is minimum 20kg and it's calibrated to stay in the same place, difficult to apply if we use the same centrifuge to all visits for all patients) It's not the same if we need to process immediately and to keep at -80ºC. At the end, we need to check every detail.
- About management of biosamples: Favouring self-sampling only for well-known/routine

practice devices (urine samples)

- When challenges with logistics and management of investigational medicinal product (IMP) and biosamples are foreseen, consider the possibility of integrating the DCT (a hybrid form, combining home based, traditional onsite visits, and study protocols)

2.C. By facilitating IMP management and temperature control

- Use automated temperature sensors for temperature-sensitive IMPs to make it obvious when temperature deviations have occurred.
- Use of an electronic device that records and stores data on when the IMP is opened and its temperature.
- Give simple instructions to the patient via a mobile phone app.
- Offer online tracking of IMP shipments to patients.
- Use smart packages with temperature control.
- Use appropriate technology/devices to track transport, delivery and administration of IMP.
- Transport the IMP or biosamples in boxes which measure the temperature/light/etc. continuously, and also upload this to a server, so that the researcher can check remotely if the correct conditions were met.

2.D. By facilitating biosample management tracking

- Use QR codes to track the sample and a way for all parties to see this information.
- Transport the IMP or biosamples in boxes which measure the temperature/light/etc. continuously, and also upload this to a server, so that the researcher can check remotely if the correct conditions were met.

2.E. Training of professionals for the new roles and delegated tasks of the DCT

- The sponsor should have professionals trained in the delegated tasks.
- Train the professionals in charge of obtaining, handling and manipulation of biological samples in good clinical laboratory practice standards and IATA.
- Ensure training is provided and then people properly understand requirements and their importance.

2.F. Using local pharmacies, pick-up points, laboratories, and healthcare centres

- Delivery of medication to the pharmacy office near the patient's home.
- Whenever possible, favour an easier environment for IMP management, i.e. the participant's local pharmacy, which mimics standard practice for outpatient treatment.
- Rethinking distributed delivery to focus on multiple small centres, rather than homes.
- Use of local labs, with shorter travel distance.
- Create a few distribution centres in the country in which the conditions can be controlled, where the participant can pick up the IMP or drop-off the biosamples. Pharmacies can be asked to act as a distribution centre.
- Include the home hospitalization professionals of the centres within the research team. Have advice from home hospitalization professionals in the design of study procedures.
- To design a logistic system to collect all samples. For example to collect the material directly at home or to identify a system of point distributed on territory (lockers).

2.G. Use of validated products and services

- Only work with qualified service providers that have the required experience to manage such shipping.
- Follow marketed products for home-based diagnostics for collection, storage and preservation.
- Use appropriate devices/technology for sample collection.
- Use certified home biological sampling kits (e.g. from the FDA) as they can be reliably used by participants themselves.

Challenge 3. *Ensuring effective collaboration with local resources.*

3.A. By reducing administrative burdens

- Pre-trial certification that does not need to be renewed or revisited with every new trial.
- Use vendors using site networks, and pre-established contracts with local resources.
- International quality standards.
- Inter-operability of data.
- Automate most processes, e.g. add sensors that measure temperature/light/etc. which inform the researchers when something's wrong, so that pharmacies or health centres don't need to check this.

3.B. By providing better training and financial resources for local healthcare professionals

- By encouraging the participation of local centres in clinical research, training their professionals in GCPs and including these professionals as members of the team.
- Financially compensate or provide more resources to centres as compensation for participation. These resources can be personnel or infrastructure.
- Implement a quality management system in these centres for trial processes and improve customer perception. This procedure could help the centre to attract other research or other clinical trials in the future.
- If these resources are performing protocol specific activities, then they will require training and closer investigator oversight. In this situation the roles should be compensated.
- Local resources should be trained and also financially compensated as well as allow them to participate in publications.
- Financial support to increase participation.
- Supporting personnel for local resources.
- Resourcing and training for local teams.
- Possibility for on-the-job training combined with easily accessible information.
- Risk-based training and risk-based implementation of legal requirements.

3.C. By providing better incentives and compensation for involvement of local resources in trials

- Refer participants to local care site when trial is completed.
- Promote special research centre identification for participating centres, e.g., with identification plaques on building facades that will result in a better perception by the public.
- Provide visibility in the system for centres that become certified as local research support centres.

- Inclusion in research group.
- Provide an incentive for pharmacies to participate. There would possibly be better participation from independent pharmacies vs. chain pharmacies. Chain pharmacies are focused on the financial numbers and pharmacists are unlikely to be motivated to provide this sort of service, whereas an independent community pharmacy may be interested in expanding its patient reach through participation as a research site. Pharmacies that are already specialty pharmacies in an area could be interested. The benefits to the specific pharmacy would need to be explored.
- Opportunities for career progression and inclusion in research.

3.D. By describing clearly the roles and functions of local partners

- Elaborate a policy for collaboration drafted through a participatory methodology with stakeholders from local settings/local resources.
- Involve members / executives from local resources to evaluate the feasibility of the proposed collaboration, and identify barriers /challenges for responsibilities and the maintenance of quality standards.
- In case no vendors are used for local resources, ensure that contracts are defined appropriately regarding roles and responsibilities. As additional contracts are required, ensure that additional workload is connected with that, so the sponsor's study team should be sufficiently resourced.
- The participation and responsibilities of the different local resources must be clearly defined and accepted/signed by the person in charge of the local resource used.
- It requires agreement by all actors. It should be specified what kind of tasks can be performed in these sites, while respecting regulations and patient confidentiality.
- Clear partnerships rather than central command and control.
- Clear description of whole process.
- Clear description of responsibilities.
- Contract between local resources and DCT centres.
- Specifications included in the contracts.

3.E. Making local health care providers (HCPs) and patients aware of the importance of research for patients

- The value of research to the participant and wide society should be reinforced. Many HCPs aren't looking for financial benefits but are looking for benefits to their patients.
- Reinforce the positive impact on health care of this type of study.
- Communicating clearly the benefits to them and to the patients. While there is some increased burden in some ways, there is decreased burden in other ways. DCTs can reach more patients, in more locations, more diversity, DCTs can help reduce dropouts and increase data collection etc.

Challenge 4. *Lack of harmonisation in the regulation and legislation.*

4.A. By developing guidelines and facilitate/stimulate? knowledge sharing among stakeholders in DCTs

- Propose an harmonised guidance, based on interdisciplinary research and stakeholder involvement.

- Get regulatory intelligence from DCT vendor at an early stage of the trial, in order to plan accordingly on a per-country basis. Avoid building internal sponsor libraries, as regulations are fluid and are changing often. Rely on regulatory intelligence from DCT vendor.
- Elaborating guidelines like the recent guideline published by the EMA. More relation between data protection lawmakers and clinical trials lawmakers is needed to provide a common law.
- As an industry working in innovation areas, we should aim to share our learnings, which should include highlighting the benefits of the European guidances.
- The sponsor should take every opportunity to comment on the planned regulatory guidelines and to participate in regulatory workshops.
- Development of common framework. Foster the establishment of a multi-stakeholder neutral platform to enable discussion.
- Multistakeholders approach (pharma, regulatory authority, public health and patients associations) to design the new procedures and regulatory frameworks in order to share a different use of DCTs.

4.B. Through gradual implementation of DCT elements incorporating adaptations to the local or national specificities.

- In the absence of homogeneity, limit the geographical scope by adapting protocols to national specificities as far as possible.
- The first step is to showcase effective DCT elements in local ECs, and drive local changes first.
- If there is absence of homogeneity, local adaptations of the research protocol should be possible, so that the protocol can be adapted for cultural/local differences.
- Carry out feasibility studies in order to identify the opportunities and the challenges from a regulatory standpoint and to favour the authorization and implementation of DCTs.

4.C. Stimulating learning and harmonisation between EU member states/ internationally

- A common EU approach sets a standard for everyone else to follow. Early release of a guidance means that others can more efficiently follow. It should be clear that no regulatory body sets out to be vastly different to other competent authorities.
- Setting up according to the most rigid legislation for now and opening up for a cross border discussion towards a common ground.
- Need for clear mapping of variation in standards.
- Increase meetings of those involved at an international level to reach agreements.
- Working groups from different countries can be set up to work in this area.
- Learning from other European Initiatives.
- Incentives to harmonise (as seen with GCP).

4.D. By centralizing clinical trial ethics review at the EU level

- A central ethical review committee and data privacy officer for all European countries would be helpful. So that the protocol needs to be submitted only once, instead of in each country separately. Although we should adhere to the same European laws, review boards interpret the laws and regulations slightly different, which might result in local adaptations of the research protocol. One review board for all European countries will save time and money for both the researchers and the review boards.

4.E. By using advanced and verifiable digital security

- Since we want to protect the integrity of patients, patients should have more say in the level of protection.
- Improve recording of all data anonymously.
- The use of advanced and verifiable digital security is essential to allow for e-signatures and protected data collection.

4.F. Through specialisation in DCT roles.

- Regarding the current variety and, in consequence, increased operational complexity: ensure to have a dedicated function in the study team for DCT element implementation

Challenge 5. *Improving on the lack of specific knowledge and accumulated experience for ethical, legal and regulatory assessment of DCTs.*

5.A. Through general knowledge-sharing, education and training for conducting DCTs

- Organise sessions or conferences inviting professionals of different profiles to give their vision and talk about their experience in participating in these studies.
- Organise practical workshops on the management and development of the different stages. Carry out practical exercises on the development of some key visits such as the inclusion of the patient with the obtaining of the IC, a follow-up visit at home with delivery of medication and biological samples... these exercises can be carried out with the help of an illustrative video.
- Promoting courses on good clinical practice in these studies.
- Promote national working groups that include professionals with these profiles to be disseminated with the help of industry and regulatory agencies.
- Promote scientific and ethical publications and research.
- Proactive sharing of lesson's learned via industry stakeholder meetings such as DIA, CTTI, local forums, etc., as well as regulator led forums such as EMA stakeholder meetings.
- Hold regular webinars/experience sharing for any stakeholders.
- Have forums at regional and national level where dialogue can take place with several Ethics Committees at the same time. This would make it easier to initiate information exchange sessions.
- Trials@Home is building a great reputation so expanding on that, potentially by attending more conferences, publishing white papers etc., creates a lot of awareness.
- Facilitate training.
- Working groups can be set up to share experience and knowledge.
- Organise dissemination seminars and training courses.
- Join cross-company initiatives. Use and promote tools developed by cross-company alliances and initiatives. E.g. MCTC ('Modernising Clinical Trial Conduct') initiative by Transcelerate, which is providing tools also promoting DCT elements at congresses.
- Making training and formation (free online courses for example).
- Organising dedicated multi-disciplinary workshops and congresses & webinars.
- Organise symposiums on DCTs that provide sufficient time for discussion, such as the one held during the PRIM&R (Public Responsibility in Medicine and Research) conference in

December 2022. This conference is aimed at Institutional Review Board personnel, who can comment on ethical considerations.
- There are other annual conferences focused on clinical trial design and execution, so repeating the message will be important as more investigators gain experience with DCT who can share and comment on the issues cited above.
- Availability of training delivered by public sector partners.
- Publication and webinars of experiences.
- Arrange training via CTIS or via EMA.
- Connect to studies with other decentralised elements, also learning from studies during COVID.

5.B. By promoting harmonisation of guidelines at European level and continuous dialogue with regulatory agencies
- Through research for adequate assessment tools and review process.
- Elaborating guidelines like the DCT EMA guideline, including the different stakeholders involved.
- Justifying why is feasible to offer some visits at home in a specific trial. Probably, we can design a check list, asking about the home conditions required, human resources needed, equipments and materials.
- Guidelines and documents endorsed at international/European level.
- Set up working groups to involve the ECs at every step- not just showcasing results but involve them early in the conversation so they can have input on the design of the studies. Try out many small pilot studies to test various elements first.
- Clear agreed standards of best practice.
- Ask for scientific advice at (centralised) regulatory authorities.
- Communicate with inspectorate institutes.
- Write guidelines for the different stakeholders, which are all in line with each other.
- Use multistakeholders approach (pharma, regulatory authority, public health and patients associations) to design the new procedures and regulatory frameworks in order to share a different use of DCTs.

5.C. By building expertise on DCTs and move towards centralised decision making.
- More centralised Ethics Boards.
- Centralise use of experts through video visits.
- Have experts oversee the team and technicians, and use triage for escalation of issues that require expertise.
- Professionalise participation in Committees.
- To provide a knowledge base for Ethics Committees.

5.D. By simplifying and optimizing technology to reduce complexity.
- Simplify and optimise technology for all parties to reduce complexity

Challenge 6. *Overcoming barriers due to the use of digital technologies.*

6.A. By developing and improving training and support for participants and caregivers
- Unless absolutely necessary and justified in the trial protocol, participants should not be excluded from trials due to technology reasons. It should be down to sponsors to offer

support for potential challenges, as far as is reasonable.

- User training can be facilitated and logistical support can be improved in the event of incidents. It is common that if the application stops working one day the patient does not use it again, with the great loss of data that this entails.
- Online help (hotline) possibility for participants to contact trial staff in case of difficulties
- Ensure proper helpdesk support (in local language!) and training of patients.
- We have to use telehealth visits to ensure correct use of the device during data collection – at least until quality is ensured. Having excellent tech support is essential – the coordinators can be taught to do some troubleshooting but it could become burdensome so the manufacturer needs to be committed to providing tech support.
- Training participants in the use of digital tools.
- Initial setup visits with participants.
- Have video explanations available for participants to consult.
- Always offer Home Health Nursing support for patients to handle DCT devices.
- Training and education courses for carers, patients and caregivers.
- Digital tutor to help the patients and caregiver to face the digital procedures.

6.B. By making sure sufficient financial and technological resources are available to participants.

- Unless absolutely necessary and justified in the trial protocol, participants should not be excluded from trials due to technology reasons. It should be down to sponsors to offer support for potential challenges, as far as is reasonable.
- Provide hotspots for people who don't have wifi (although that doesn't solve the problem of poor mobile phone service in remote areas).
- Providing devices (tablets) to participants to use for telehealth and data entry.
- Making them sign a contract before giving them an expensive electronic device stating that they will take good care of the device while participating in the study.
- Helping participants delete study applications from the device after the study is over.
- Compensation to participants (electricity e.g. if we need to connect the centrifuge or other equipment) or for using their laptop.
- Provide devices to participants so that they do not have to own one.
- Encourage staggered recruitment of patients when the use of the devices is essential, providing the centre with a certain number of devices that have to be reused by several patients.
- If trial participants are baring the costs of technology, these must be reimbursed. We should also pay upfront and not expect participants to be out of pocket.
- Sponsor must provide all the devices to patients. Any expense must be reimbursed.
- To prepare a budget considering all extra human and materials, taking into account that we have less costs related to the use of hospital facilities.
- Decrease costs: let participants bring their own device. Ask developers to provide their devices/apps for free and in return give them the (anonymous) data.
- Provision of local community internet hubs/signal boosts associated with the trial (and that remain afterwards).
- Specific assurance in order to guarantee the digital protection of people.
- To decrease the economic burden for patients and caregivers on digital health (internet, device, assurance, protection procedure, privacy and digital security).

- To decrease the digital divide in particular on privacy and cybersecurity for people.

6.C. By making on-site/offline alternatives to decentralised elements available.

- Don’t force participants to DCT. The participant should always have the choice to perform assessments also on-site, depending on the patient's preference. The individual patient needs should be in the focus. There is no 'one size fits all'.
- If the problem is the electronic connection, we can use paper as source document in some places.
- If the participants prefers, we can offer the use of classic consent instead of eConsent.
- Plan the eConsent discussion always with a televisit, or offer the patient a face to face on-site discussion (depending on patient's preference).
- Let participants device how to communicate using their preferred method (e.g. video calls, phone calls, visits).

6.D. By simplifying and adapting technology for participants’ ease of use

- Use of older, more available technology.
- Make sure devices work without internet. For example save data offline and upload once internet connection is established.
- Make the study procedures easy to understand and provide a manual.
- Assess case by case specific challenges related to vulnerable groups and the use of technologies, including in advance the assess of potential digital divide, etc.
- Encourage the use of patient devices and favour the design of open source or free format programs. Guarantee security measures in these cases.
- Feedback to tech companies/OS developers to maintain backwards compatibility.

6.E. By ensuring data quality of remote/digital technologies used in DCTs

- Optimize web portals for data collection.
- Use devices with CE mark.
- Data Protection Impact Assessment is needed.
- Real-time data monitoring so that researcher can intervene in time. Start data analyses early (after couple of participants are finished), so that possible mistakes can be identified early in the data collection process. Make sure that the researchers and participants have to do as little as possible, i.e., automate all processes as much as possible to prevent human errors.
- Improved technology to identify device failure.
- Make the measurement time as long as possible to reduce signal/noise ratio.

6.F. Through local resources involvement.

- Seek the support of local centres for these procedures.
- Provision of local community internet hubs/signal boosts associated with the trial (and that remain afterwards).
- Hospitals must provide adequate spaces and a good connectivity.

6.G. By centralising the DCT elements used in a single vendor

- Use only 1 DCT vendor for all DCT elements, to avoid patients struggling with several systems/log in data.

6.H. By ensuring that discussion between the researcher and the potential participant is maintained as part of the informed consent process.

- It is an important aid to obtain informed consent, always understanding that it is an aid. A member of the research team must always be present to answer questions.
- Electronic consents that are simply digital forms of paper documents are insufficient in and of themselves for adequate informed consent. Ensure that a face-to-face conversation (includes just telephone but telehealth is now preferred) occurs prior to signing consents. This ensures that the participant fully understands the commitment and reduces lost to follow-up.
- Provide the participant with the signed forms either digitally or hard copy mailed to them.
- Virtual real time-face to face discussion, common informative sessions.
- Be very transparent about our DCTs to participants and proactively discuss expectation and potential challenges. The more participants understand what is expected from the outset, the less impact issues that do arise will have.
- All the information must be included in the information sheet signed remotely or using the print-to-sign method.

Annex 3. Results of the assessment of the appropriateness given by the panellists to each proposal to overcome the main challenges of DCTs.

Decentralised clinical trials may increase the burden or risk-taking for the health care providers									
Proposal	By developing and improving training and support.	By tailoring trial set-up to DCT elements.	By improving collaboration and involvement of all parties involved in trial conduct.	Through development and selection of more adequate and standardised technology.	By ensuring remote follow-up of the safety of participants.	Through the development of a risk mitigation/management plan by the sponsor.	By paying more attention to trial safety conditions	Through automation of trial procedures.	By facilitating peer-to-peer support among participants.
Mean	3.67	3.31	3.24	3.22	3.17	3.12	3.11	2.88	2.19
Standard deviation	0.49	0.48	0.56	0.43	0.62	0.70	0.68	0.86	0.83
Median	4	3	3	3	3	3	3	3	2
Four	12	5	5	4	5	5	5	5	1
Three	6	11	11	14	11	9	10	5	4
Two	0	0	1	0	2	3	3	7	8
One	0	0	0	0	0	0	0	0	3
Total	18	16	17	18	18	17	18	17	16
1/N%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	18.8%
2/N%	0.0%	0.0%	5.9%	0.0%	11.1%	17.6%	16.7%	41.2%	50.0%
3/N%	33.3%	68.8%	64.7%	77.8%	61.1%	52.9%	55.6%	29.4%	25.0%
4/N%	66.7%	31.3%	29.4%	22.2%	27.8%	29.4%	27.8%	29.4%	6.3%
Essential (3+4)	18	16	16	18	16	14	15	10	5
Not essential (1+2)	0	0	1	0	2	3	3	7	11
Essential/N%	100%	100%	94%	100%	89%	82%	83%	59%	31%
Not essential/N%	0%	0%	6%	0%	11%	18%	17%	41%	69%

Preventing challenges with logistics and management of investigational medicinal product (IMP) and biosamples							
Proposal	Use of validated products and services.	By facilitating IMP management and temperature control.	By developing training and providing support to participants regarding use of medication and collection of biosamples.	By adapting the study protocol to the therapeutic area, participant characteristics and study procedures.	By facilitating BioSample management tracking.	Training of professionals for the new roles and delegated tasks of the DCT.	Using local pharmacies, pick-up points, laboratories and healthcare centers.
Mean	3.59	3.39	3.33	3.29	3.29	3.28	3.22
Standard deviation	0.62	0.50	0.59	0.59	0.59	0.46	0.73
Median	4	3	3	3	3	3	3
Four	11	7	7	6	6	5	7
Three	5	11	10	10	10	13	8
Two	1	0	1	1	1	0	3
One	0	0	0	0	0	0	0
Total	17	18	18	17	17	18	18
1/N%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2/N%	5.9%	0.0%	5.6%	5.9%	5.9%	0.0%	16.7%
3/N%	29.4%	61.1%	55.6%	58.8%	58.8%	72.2%	44.4%
4/N%	64.7%	38.9%	38.9%	35.3%	35.3%	27.8%	38.9%
Essential (3+4)	16	18	17	16	16	18	15
Not essential (1+2)	1	0	1	1	1	0	3
Essential/N%	94%	100%	94%	94%	94%	100%	83%
Not essential/N%	6%	0%	6%	6%	6%	0%	17%

Ensuring effective collaboration with local resources					
Proposal	Making local HCPs and patients aware of the importance of research for patients.	By reducing administrative burdens.	By providing better training and financial resources for local healthcare professionals.	By describing clearly the roles and functions of local partners .	By providing better incentives and compensation for involvement of local resources in trials.
Mean	3.50	3.39	3.39	3.39	3.17
Standard deviation	0.52	0.61	0.50	0.61	0.79
Median	3.5	3	3	3	3
Four	8	8	7	8	7
Three	8	9	11	9	7
Two	0	1	0	1	4
One	0	0	0	0	0
Total	16	18	18	18	18
1/N%	0.0%	0.0%	0.0%	0.0%	0.0%
2/N%	0.0%	5.6%	0.0%	5.6%	22.2%
3/N%	50.0%	50.0%	61.1%	50.0%	38.9%
4/N%	50.0%	44.4%	38.9%	44.4%	38.9%
Essential (3+4)	16	17	18	17	14
Not essential (1+2)	0	1	0	1	4
Essential/N%	100%	94%	100%	94%	78%
Not essential/N%	0%	6%	0%	6%	22%

Lack of harmonisation of the regulation and legislation						
Proposal	By developing guidelines and knowledge sharing among stakeholders in DCTs.	Stimulating learning and harmonisation between EU member states / internationally.	Through gradual implementation of DCT elements incorporating adaptations to the local or national specificities.	By using advanced and verifiable digital security.	Through specialisation in DCT roles.	By centralizing clinical trial ethics review at the EU level.
Mean	3.71	3.41	3.40	3.19	3.06	2.76
Standard deviation	0.47	0.51	0.51	0.75	0.75	0.75
Median	4	3	3	3	3	3
Four	12	7	6	6	5	3
Three	5	10	9	7	8	7
Two	0	0	0	3	4	7
One	0	0	0	0	0	0
Total	17	17	15	16	17	17
1/N%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2/N%	0.0%	0.0%	0.0%	18.8%	23.5%	41.2%
3/N%	29.4%	58.8%	60.0%	43.8%	47.1%	41.2%
4/N%	70.6%	41.2%	40.0%	37.5%	29.4%	17.6%
Essential (3+4)	17	17	15	13	13	10
Not essential (1+2)	0	0	0	3	4	7
Essential/N%	100%	100%	100%	81%	76%	59%
Not essential/N%	0%	0%	0%	19%	24%	41%

Improving on the lack of specific knowledge and accumulated experience for ethical, legal and regulatory assessment of DCTs				
Proposal	By promoting harmonisation of guidelines at European level and continuous dialogue with regulatory agencies.	Through general knowledge-sharing, education and training for conducting DCTs.	By simplifying and optimizing technology to reduce complexity.	By building expertise on DCTs and move towards centralised decision making.
Mean	3.71	3.47	3.33	3.18
Standard deviation	0.47	0.72	0.72	0.64
Median	4	4	3	3
Four	12	10	7	5
Three	5	5	6	10
Two	0	2	2	2
One	0	0	0	0
Total	17	17	15	17
1/N%	0.0%	0.0%	0.0%	0.0%
2/N%	0.0%	11.8%	13.3%	11.8%
3/N%	29.4%	29.4%	40.0%	58.8%
4/N%	70.6%	58.8%	46.7%	29.4%
Essential (3+4)	17	15	13	15
Not essential (1+2)	0	2	2	2
Essential/N%	100%	88%	87%	88%
Not essential/N%	0%	12%	13%	12%

Overcoming barriers due to the use of digital technologies								
Proposal	By developing and improving training and support for participants and caregivers.	By making sure sufficient financial and technological resources are available to participants.	By simplifying and adapting technology for participants' ease of use.	By ensuring that discussion between the researcher and the potential participant is maintained as part of the informed consent process.	By making on-site/offline alternatives to decentralised elements available	By ensuring data quality of remote/digital technologies used in DCTs.	By centralising the DCT elements used in a single vendor	Through local resources involvement.
Mean	3.71	3.65	3.53	3.41	3.35	3.31	2.75	2.69
Standard deviation	0.47	0.49	0.52	0.62	0.70	0.60	0.77	0.87
Median	4	4	4	3	3	3	3	3
Four	12	11	8	8	8	6	2	3
Three	5	6	7	8	7	9	9	6
Two	0	0	0	1	2	1	4	6
One	0	0	0	0	0	0	1	1
Total	17	17	15	17	17	16	16	16
1/N%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	6.3%	6.3%
2/N%	0.0%	0.0%	0.0%	5.9%	11.8%	6.3%	25.0%	37.5%
3/N%	29.4%	35.3%	46.7%	47.1%	41.2%	56.3%	56.3%	37.5%
4/N%	70.6%	64.7%	53.3%	47.1%	47.1%	37.5%	12.5%	18.8%
Essential (3+4)	17	17	15	16	15	15	11	9
Not essential (1+2)	0	0	0	1	2	1	5	7
Essential/N%	100%	100%	100%	94%	88%	94%	69%	56%
Not essential/N%	0%	0%	0%	6%	12%	6%	31%	44%